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Rh-Catalyzed Reductive Coupling under Hydrogenation Conditions and Nucleophilic Catalysis *via* Phosphine Conjugate Addition

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Rh-Catalyzed Reductive Coupling under Hydrogenation Conditions and Nucleophilic Catalysis *via* Phosphine Conjugate Addition

by

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Dissertation

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Dedication

To my parents, my wife Eunha Song, and my son Michael Kyungbin Kong

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A journey is always easier when you travel together. In the following list there are a number of people to whom I would like to express my deepest gratitude for their support during my Ph.D. First of all, I would like to thank my supervisor Professor Michael J. Krische for giving me the opportunity to come to UT at Austin, for teaching me how good research is conducted, and for sharing his great knowledge of chemistry. In many ways, it has been a great experience to work in his group for the last five years.

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I would like to give my special thanks to my wife Eunha Song who is my permanent anger manager and my son Michael Kyungbin Kong who is a future scientist. I am very sorry that there is no suitable word to express my deepest gratitude for my parents. I love you!

Rh-Catalyzed Reductive Coupling under Hydrogenation Conditions and Nucleophilic Catalysis *via* Phosphine Conjugate Addition

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At the threshold of the 21st centry, a new set of challenges is defined by the need to develop sustainable means of preparing chemical commodities demanded by society. Hence, such concepts as atom economy, step economy, and 'green chemistry' have become the requirements for the development of synthetic reactions. Hydrogenation is one of the most powerful catalytic methods which successfully satisfy the stated requirements of modern chemistry. Accordingly, catalytic hydrogenation has been tremendously utilized in industrial settings. The profound impact of hydrogenation portended a powerful approach to reductive carbon-carbon bond formation under hydrogenation conditions, resulting in the discovery of the Fischer-Tropsch process and hydroformylation. However, since this discovery, processes have restricted to the incorporation of a single carbon monoxide unit. Even though there are a few seminal contributions, systematic efforts toward the development of hydrogen-mediated carbon-carbon bond forming processes beyond hydroformylation have been absent from the

literature. In an exciting advance, the Krische group has shown that it is possible to reductively couple two or more organic molecules simply through their exposure to gaseous hydrogen in the presence of a metal catalyst. This finding has led to the development of a broad, new family of hydrogen-mediated C-C bond formation. Herein, related to hydrogen-mediated C-C bond formation, the overview of metal catalyzed intermolecular reductive coupling in the presence of reducing agents such as borane, silane, alane, metal, and hydrogen is presented. Chapter 2 describes systematic approaches to the development of hydrogen-mediated C-C bond formation and successful preliminary results achieved by our research group. Chapters 3 and 4 will describe the further extension of these hydrogen-mediated C-C bond formations including (1) hydrogen-mediated reductive couplings of conjugated alkynes with iminoacetates, (2) hydrogen-mediated reductive couplings of 1,3-enynes with α-ketoesters, and (3) hydrogen-mediated multicomponent reductive couplings.

The development of catalytic systems for the nucleophilic activation of enones using phosphine catalysts has received attractive attention. Recently, an intramolecular variant of the Rauhut-Currier reaction was developed in our lab. To further extend nucleophilic phosphine catalysis, we have sought to develop new catalytic methodology *via* phosphine conjugate addition. Chapter 5 describes two new methodologies related to their area: (1) catalytic cycloallylation *via* nucleophilic phosphine catalysis and (2) allylic amination of Morita-Baylis-Hillman acetates.

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Chapter 1 Metal-Catalyzed Intermolecular Reductive Coupling

1.1 INTRODUCTION AND SCOPE

The catalytic reductive coupling is one of the most important methods for carbon-carbon bond formation. The representative catalytic reductive coupling reactions such as the Fischer-Tropsch process (1922)[1] and hydroformylation (1938)[2] are industrially important methods of carbon-carbon bond formation[3]. The concept of reductively coupling two or more small molecules to form larger or complex molecule has been appealing to synthetic chemists due to its atom ecomomy[4] and environmentally friendly nature. The Takahashi group (1969)[5a] and the Tsuji group (1971)[5b] independently discovered a novel palladium catalyzed hydrosilylation of butadiene, making the first "non-hydrogen-mediated" reductive coupling reaction. Since this discovery, catalytic reductive coupling reactions have only recently attracted a high level of interest in the formation of carbon-carbon bonds in synthetic as well as industrial circles. Progress has been made with regard to the nucleophilic activation of diverse precursors containing π-bonds such as alkenes, alkynes, enones, dienes, and enynes, then catalytically reductively coupling those to other partners containing π-bonds.

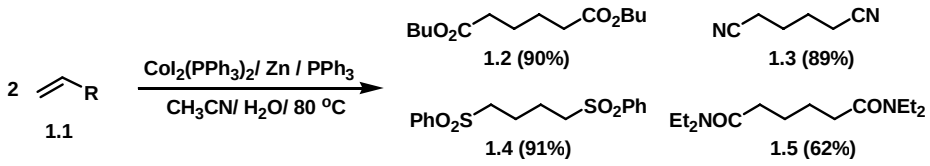
Some of important examples of reductive couplings include the Fischer-Tropsch reaction and hydroformylation[6], the reductive Heck reaction[7], the reductive aldol reaction[8-11], Nozaki-Hiyama-Kishi coupling[12], reductive cyclization[13], reductive coupling of two π components, and pinacol coupling[14]. Recently, catalytic intermolecular reductive coupling reactions have received substantial attention. The following review will discuss the advent and development of one of the most attractive synthetic methods. This review is organized by catalyst system and substrate functionality.

Classical reactions such as the Fischer-Tropsch process and hydroformylation however, will not be covered. Reductive cyclizations (intramolecular reductive coupling) and the reductive aldol reaction will also not be covered. Additionally, reactions including the activation of a carbon-halogen bond such as the Nozaki-Hiyama-Kishi coupling and reductive Heck coupling are beyond the scope of this review.

1.2 REDUCTIVE COUPLING OF ALKENES WITH ALKENES, ALKYNES, OR ANHYDRIDES

1.2.1 Alkene-Alkene Coupling

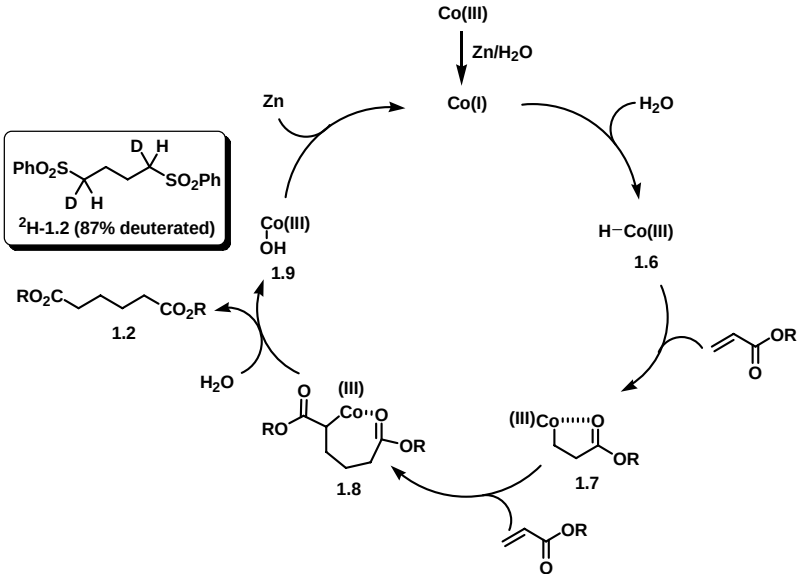
Transition metal-catalyzed dimerization of olefins is useful for synthesizing important intermediates for fine and industrial chemicals.[15] In 2004, the Cheng group reported the cobalt-catalyzed reductive dimerization of alkenes. Butyl acrylate in the presence of $CoI_2(PPh_3)_2$, PPh_3, zinc metal powder and water in acetonitrile at 80 ^oC underwent tail-to-tail reductive dimerization to give dibutyl adipate **1.2** in 90% yield with complete regioselectivity.[16] Acrylonitrile, phenyl vinyl sulfone, and acrylamide were also reductively dimerized to give the corresponding dimers **1.3-1.5** (Scheme 1.1).



Scheme 1.1 Co-catalyzed reductive dimerization of alkenes.

It was found that the choice of solvent is vital to the catalytic reaction. Upon screening of a variety of solvents, acetonitrile proved most effective. Dichloromethane, THF, and DMF are less effective providing **1.2** in 63%, 33%, and 26% yields, respectively. Interestingly, toluene is completely ineffective providing no reductive

dimerization product. Based on the deuterium labeling study, a plausible mechanism was proposed. The catalytic cycle is initiated by the reduction of the Co(III) complex to a Co(I) complex. Protonation of Co(I) species by water generates a Co(III) hydride **1.6**. The insertion of an acrylate gives five-membered ring species **1.7**. Insertion into a second acrylate molecule provides intermediate **1.8**. Finally, protonation of Co-enolate **1.8** provides the reductive dimerization product and cobalt hydroxide complex **1.9** (Scheme 1.2).

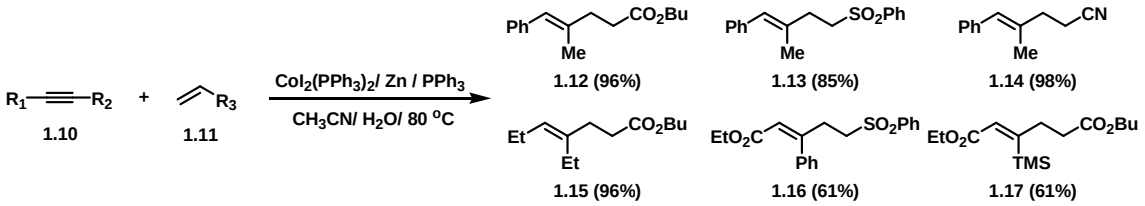


Scheme 1.2 Proposed catalytic cycle for Co-catalyzed reductive dimerization of alkenes.

1.2.2 Alkene-Alkyne Coupling

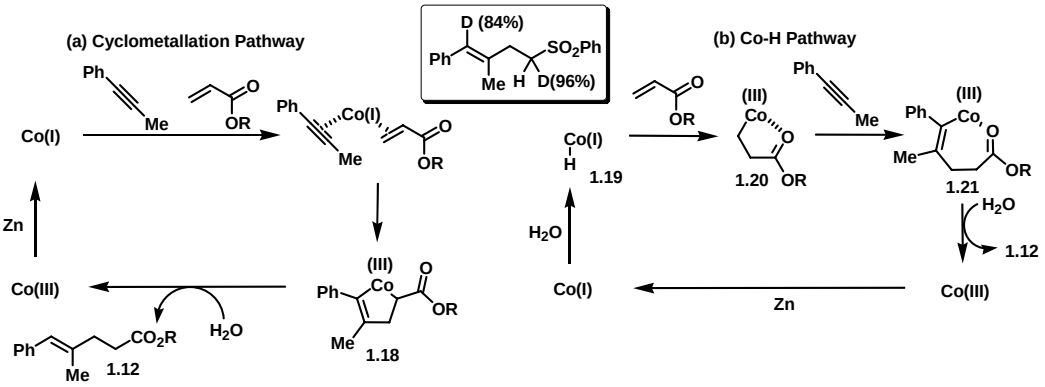
Intermolecular coupling of a carbon-carbon triple bond and double bond provides a convenient route for carbon-carbon bond formation. Due to the regio- and stereoselectivity problems and potential side reactions such as cyclotrimerization[17] and polymerization, there was no catalytic intermolecular reductive ene-yne coupling until 2002. Here, the Cheng group reported a cobalt-catalyzed highly regioselective and

stereoselective intermolecular reductive coupling of alkynes with conjugated alkenes in 2002.[18] Treatment of alkyne **1.10** with a variety of activated alkenes **1.11** in the presence of $Co(Ph_3)_2I_2$, PPh_3, water, and zinc metal powder in acetonitrile at 80 ^oC led to reductive coupling of alkyne and activated alkene to give products **1.12 – 1.17** in good to excellent yields (Scheme 1.3).



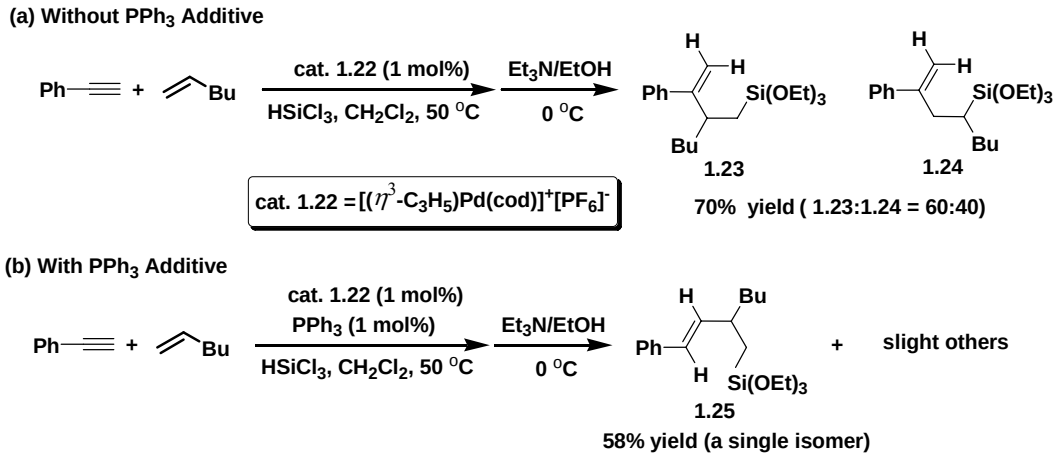
Scheme 1.3 Co-catalyzed reductive cupling of alkenes and alkynes.

The author proposed two possible mechanisms based on the known organometallic chemistry that relates to acrylates and alkynes as well as a deuterium isotope-labeling experiment. The first proposed mechanism includes the formation of cobaltacyclopentene intermediate **1.18** from oxidative coupling of an alkyne and an alkene to the cobalt(I) center followed by protonation of the intermediate **1.18**[19] by water (Scheme 1.4 (a)). Another possible mechanism involves a cobalt(III) hydride **1.19** generated from protonation of cobalt(I) by water. Insertion of an acrylate molecule into the cobalt hydride **1.19** gives five-membered ring species **1.20**. Further insertion of an alkyne molecule gives cobalt(III) intermediate **1.21**. Subsequent protonation of **1.21** produces the reductive coupling product **1.12** and regenerates the Co(I) complex (Scheme 1.4 (b)).



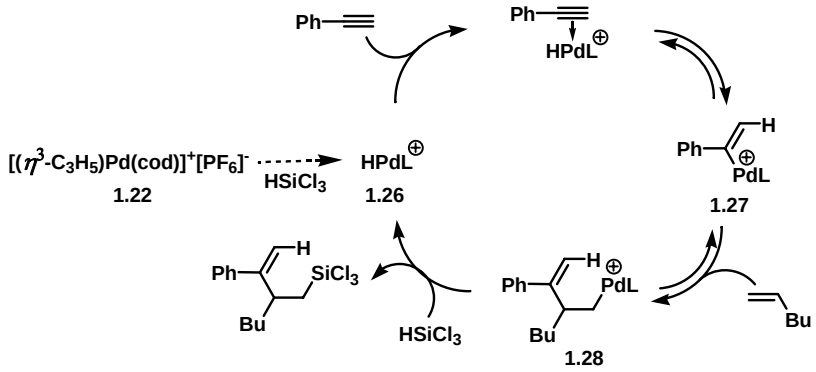
Scheme 1.4 Proposed catalytic cycles for reductive coupling of alkenes and alkynes.

In 2005, the Yamamoto group reported a cationic palladium-catalyzed hydrosilylative cross-coupling of alkynes with alkenes.[20] Exposure of the mixture of phenyl acetylene and 1-hexene (3 equiv.) to trichlorosilane in the presence of catalytic cationic palladium (II) **1.22** afforded the coupling products **1.23** and **1.24** in 70% combined yield as triethoxysilyl derivatives after a usual work-up (Scheme 1.5 (a)). Additionally, they discovered that triphenylphosphine greatly affected the regioselectivity of the reaction. Once triphenylphosphine (1equiv.) was added to catalyst **1.22**, the same reaction shown in Scheme 1.5 (a) exhibited a different reaction pattern to afford a single coupling product **1.25** in 58% yield (Scheme 1.5 (b)).



Scheme 1.5 Cationic Pd-catalyzed hydrosilylative cross-coupling.

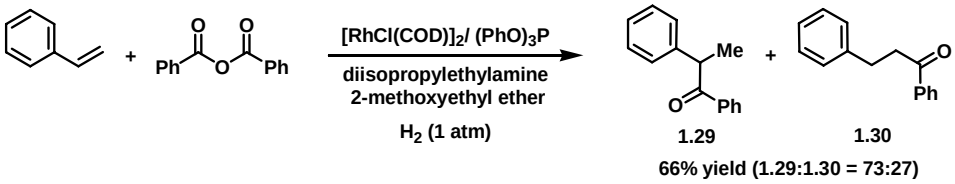
Mechanistically, the reaction with cationic palladium and trichlorosilane would produce a palladium hydride complex **1.26**. Next, hydropalladation of a given alkyne would afford alkenylpalladium intermediate **1.27**, which would undergo rapid and regioselective alkene insertion to generate homoallylic organopalladium intermediate **1.28**. Finally, the resulting organopalladium **1.28** would terminate one catalytic cycle by undergoing substitution at the palladium center with a trichlorosilyl group (Scheme 1.6).



Scheme 1.6 Proposed catalytic cycle for Pd-catalyzed hydrosilylative cross-coupling.

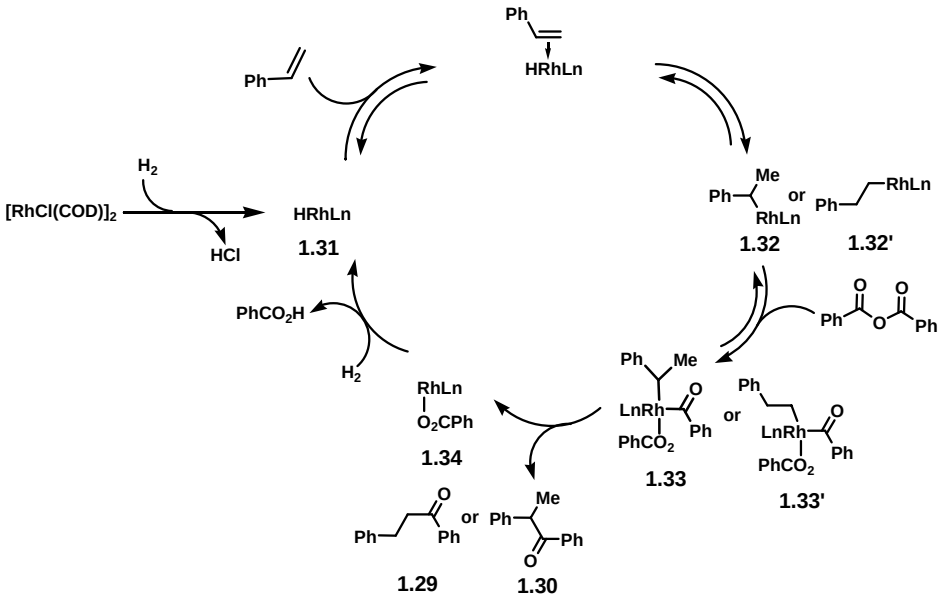
1.2.3 Alkene-Anhydride Coupling

In 1995, the Miura group reported rhodium-catalyzed reaction of benzoic anhydride with styrene at atmosphere of molecular hydrogen.[21] The reaction of benzoic anhydride with styrene in the presence of $[RhCl(COD)]_2$, $(PhO)_3P$, and diisopropylethylamine in 2-methoxyethyl ether at 65 ^oC under 1 atm of molecular hydrogen gave 1,2-diphenyl-1-propaneone **1.29** as the major product along with 1,3-diphenyl-1-propanone **1.30** in 66% yield (Scheme 1.7).



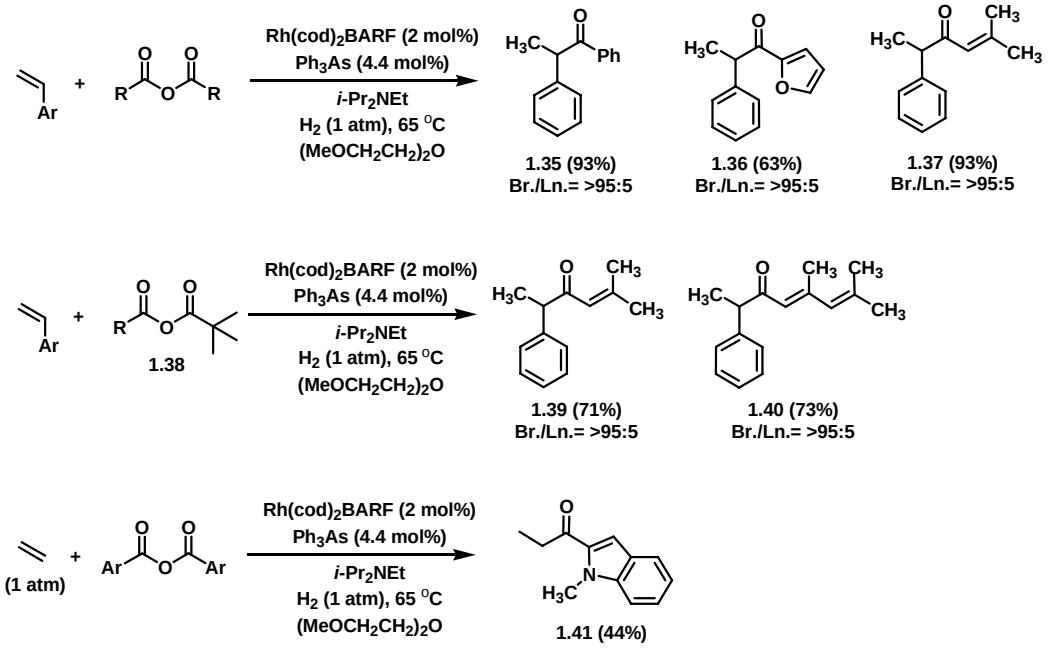
Scheme 1.7 Rh-catalyzed reductive coupling of alkenes and anhydrides.

On the basis of the deuterium labeling study and the product ratio analysis, a plausible mechanism was proposed. The catalytic cycle is initiated by reaction of $[RhCl(COD)]_2$ with hydrogen in the presence of $(PhO)_3P$ and a base to generate a hydridorhodium species **1.31**. Insertion of styrene to intermediate **1.31** affords two different rhodium complexes **1.32** and **1.32'**, each undergoes oxidative addition of benzoic anhydride to produce two rhodium complexes **1.33** and **1.33'**. Reductive elimination of rhodium complexes **1.33** and **1.33'** would produce the corresponding products (**1.29** and **1.30)** and benzoyloxyrhodium species **1.34** which may react with hydrogen to regenerate the hydridorhodium complex (Scheme 1.8).



Scheme 1.8 Proposed catalytic cycle for reductive coupling of alkenes and anhydrides.

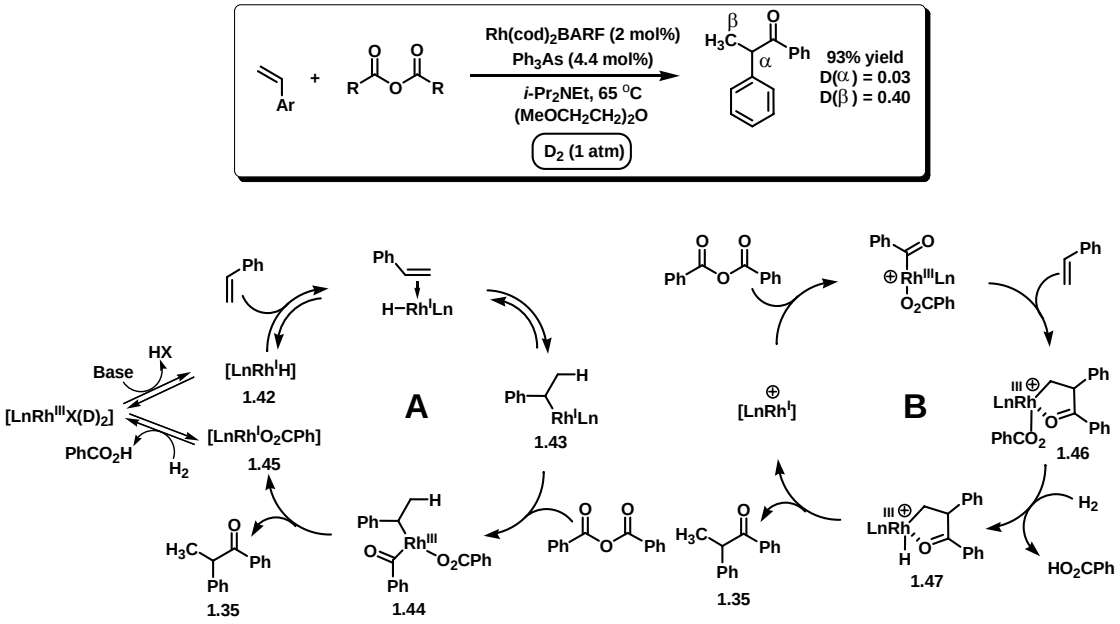
Recently, the Krische group reported an advanced catalyst system for hydrogen-mediated alkene-anhydride coupling. They found that cationic rhodium catalysts ligated by triphenylarsine (Ph_3As) enable formation of branched hydroacylation products (**1.35 - 1.37**) with exceptionally high levels of regiocontrol. For more precious carboxylic acids, they also showed that selective acyl transfer from mixed anhydrides **1.38** was possible to produce completely branch-selective hydroacylation product **1.39** in good yields. In addition, reductive coupling of ethylene in the presence of carboxylic anhydride **1.40** produced the corresponding ethyl ketone **1.41** in 44% yield (Scheme 1.9).[22]



Scheme 1.9 Cationic Rh-catalyzed reductive coupling of alkenes and anhydrides.

On the basis of a deuterium labeling study, two possible mechanisms were proposed. In catalytic mechanism **A**, the catalytic cycle is initiated by the reaction of the cationic rhodium complex with molecular hydrogen in the presence of Ph_3As and a base to generate a hydridorhodium species **1.42**. Subsequent hydrometallation of styrene

delivers organorhodium intermediate **1.43** which engages in formal acyl substitution to produce intermediate **1.44**. Finally, C-C reductive elimination produces the hydroacylation product **1.35** and rhodium carboxylate complex **1.45**. In catalytic mechanism **B**, oxidative addition of anhydride followed by insertion of styrene affords organorhodium intermediate **1.46**. Subsequent hydrogenolysis of intermediate **1.46** delivers hydridorhodium complex **1.47**. C-H reductive elimination produces the hydroacylation product **1.35** (Scheme 1.10).



Scheme 1.10 Proposed mechanisms for cationic Rh-catalyzed reductive coupling.

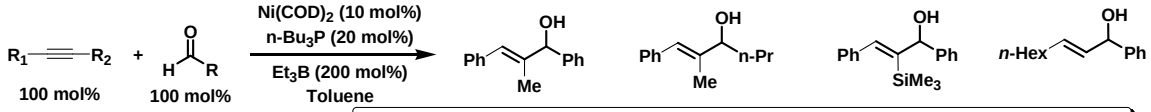
1.3 REDUCTIVE COUPLING OF ALKYNES WITH CARBONYLS

Allylic alcohols are organic substructures which are exceptionally valuable in many synthetic applications.[23] Perhaps the most commonly used method involves coupling of alkenyl halides and aldehydes either by metallation/addition or Nozaki-Hiyama-Kishi coupling[12]. More recently, Wipf and Oppolzer demonstrated alkyne

hydrozirconation or hydroboration followed by addition to aldehydes.[24] However, many of these strategies for preparing allylic alcohols require the use of stoichiometric reagents.[25] Recent progress has shown that these versatile intermediates can be prepared *via* catalytic intermolecular reductive coupling technology.

1.3.1 Ni-Borane System

In 2000, Jamison and coworkers reported the first catalytic intermolecular reductive coupling of alkynes and aldehydes.[26] Optimal conditions to control the reactivity, stereoselectivity, and regioselectivity were determined to be reaction of 1 equiv. of aldehyde with 1 equiv. of the alkyne and a low-valent nickel catalyst along with tributylphosphine and triethylborane. The efficiency, substrate scope, and selectivity of the reaction are summarized in Scheme 1.11.

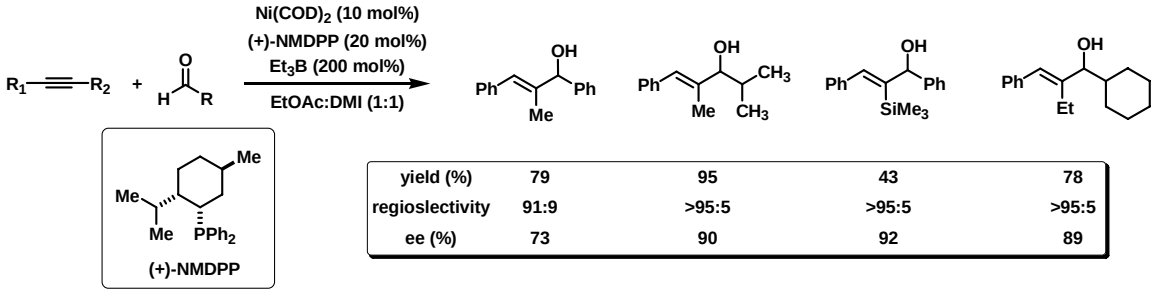


yield (%)	77	85	49	76
regioslectivity	92:8	92:8	>98:2	96:4

Scheme 1.11 Ni-Catalyzed reductive coupling of alkynes and aldehydes.

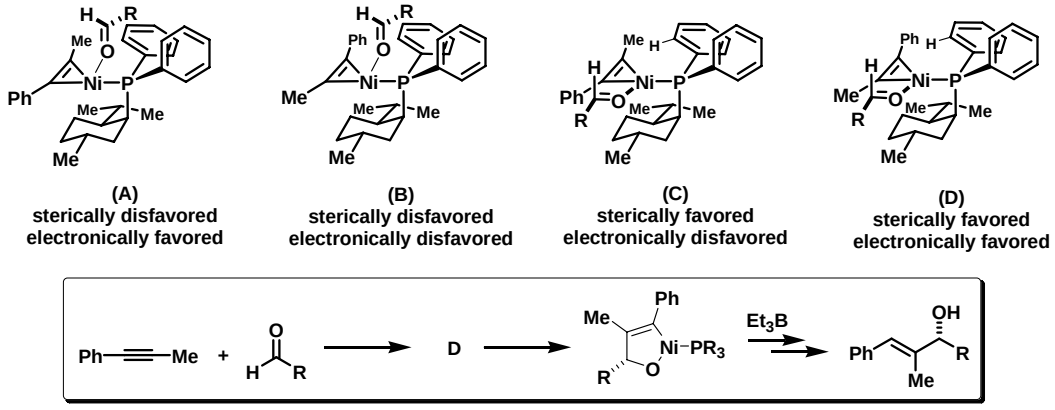
Chiral allylic alcohols are useful starting materials and are prevalent in complex natural products.[23c, 27] In 2003, the Jamison group reported the first highly enantio-selective catalytic intermolecular reductive coupling of alkynes and aldehydes.[28] From extensive evaluations of chiral ligands, transition metals, and reducing agents, they found that NMDPP, $Ni(COD)_2$, and triethylborane provided superior results. Yield and enantioselectivity were further improved by using a solvent composed of equal volumes of ethyl acetate and 1,3-dimethylimidazolidinone (DMI) in conjunction with slow

addition of the aldehyde. The catalytic system afforded trisubstitued allylic alcohols corresponding to exclusive *cis* addition to the alkyne in excellent regioselectivity and with good to excellent enantioselectivities (Scheme 1.12).[28b]



Scheme 1.12 Ni-catalyzed asymmetric reductive coupling of alkynes and aldehydes.

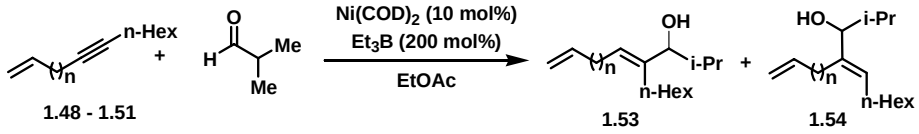
The stereochemical outcome of the asymmetric coupling with NMDPP as the chiral ligand has been rationalized by a cooperative effect between steric properties of the ligand and electronic differences of the alkyne substituents. Among four possible modes of aldehyde coordination, **A** and **C** are inconsistent with the sense and degree of regioselectivity, and **D** is more accessible and leads to the major enantiomer observed (Scheme 1.13).



Scheme 1.13 Proposed steric and electronic control in asymmetric reaction.

To achieve the regioselective coupling reactions between aldehydes and alkynes with two linear aliphatic groups, the Jamison group examined ligand-switchable directing effects[29] of tethered alkenes (**1.48-1.51**) in nickel-catalyzed additions to alkynes (Table 1.1, entries 1-4).[30] Remarkably, they found that a tether of three methylene units provided complete selectivity for allylic alcohol regioisomer **1.53** (Table 1.1, entry 3). The directing effects of tethered alkenes were further supported by a control experiment with the corresponding alkyne **1.52** lacking the pendant alkene, which gave no regioselectivity (Table 1.1, entry 4).[30a]

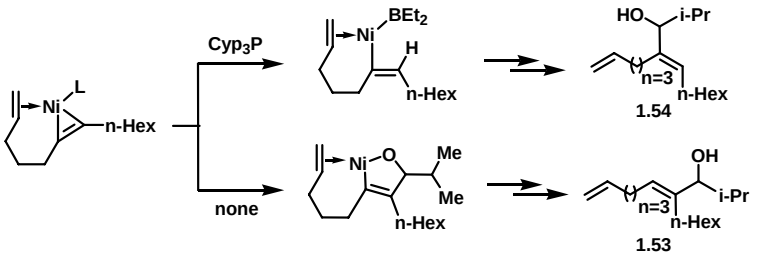
Table 1.1 Directing effects of tethered alkenes.



entry	alkyne	n	yield (%)	regioselectivity (1.53 : 1.54)
1	1.48	1	<5	nd
2	1.49	2	<5	nd
3	1.50	3	53	>95:5
4	1.51	4	<5	nd
5	n-pentyl−C≡C−n-hexyl (1.52)	n.a.	28	50:50

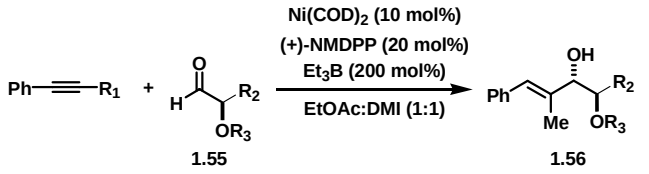
Additionally, they found that the sense of regioselectivity was completely reversed upon the addition of catalytic amount of tricyclopentylphosphine (Cyp_3P). The ligand effects provided significant insight into the mechanistic framework for the nickel-catalyzed reductive coupling reaction of alkynes in general. When Cyp_3P is employed in the reaction, the alkenyl H is installed prior to carbon-carbon bond formation to form the regioisomer **1.54** exclusively. On the other hand, in the absence of Cyp_3P, carbon-carbon bond formation occurs prior to alkenyl H introduction to produce the regioiosmer **1.53** predominantly (Table 1.2).

Table 1.2 Additive effects of regiochemistry control.



Additive	regioselectivity (1.53 : 1.54)
none	>95:5
Cyp_3P (20mol%)	5:>95

Recently, the Jamison group developed a nickel-catalyzed reductive coupling of alkynes and easily accessible, enantiomerically enriched α-oxyaldehydes **1.55**. The reductive coupling reaction provides efficient access to a variety of differentially protected *anti*-1,2-diols **1.56** (Scheme 1.14).[31]



entry	R_1	R_2	R_3	dr	yield(%)
1	Me	Cy	MOM	90:10	87
2	Et	Cy	MOM	>95:5	54
3	Et	Cy	PMB	>95:5	74
4	Et	Ph	MOM	>95:5	39

Scheme 1.14 Ni-catalyzed reductive coupling of alkynes and chiral aldehydes.

The *anti*-diastereoselectivity could be rationalized by the "dipolar" model because of the absence of any chelating metal in the reaction (Scheme 1.12).

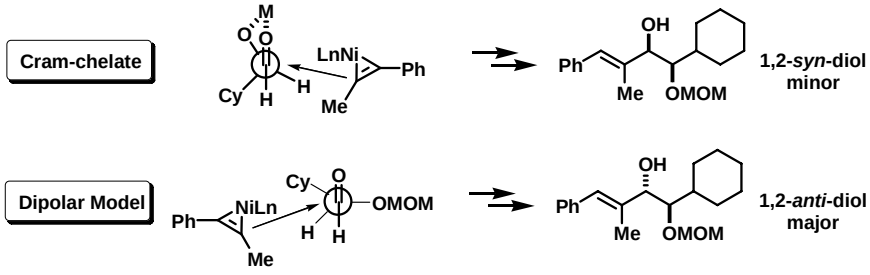
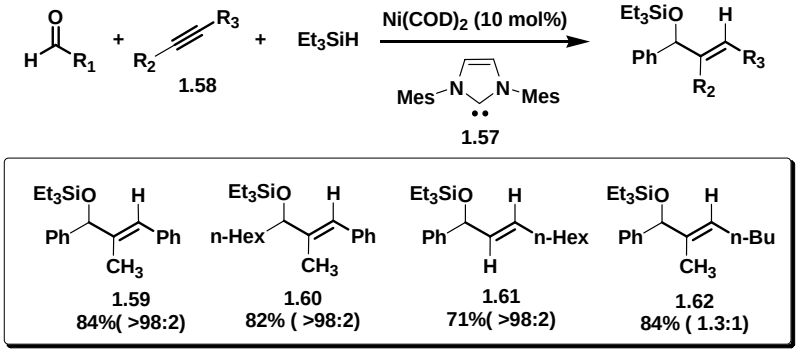


Figure 1.1 Possible interpretation of the diastereoselectivity.

1.3.2 Ni-Silane System

In 2004, the Montgomery group reported the nickel-catalyzed intermolecular reductive coupling of alkynes and aldehydes using an imidazolium carbene ligand **1.57** and triethylsilane.[32] Optimized conditions involved syringe drive addition of the alkyne (typically over 15 min). The scope of this reductive coupling method was broad, and good to excellent yields and regioselectivities were observed across a broad range of substrates **1.58**. Aromatic (**1.59**, **1.61**, and **1.62**) and aliphatic aldehydes (**1.60**) were excellent participants in the procedure. However, an internal aliphatic alkyne provided the coupling product **1.62** with low dr. It is noteworthy that this terminal alkynyl compounds were coupled to produce product **1.61** in 71% yield. Terminal alkynes were previously problematic due to alkyne trimerization (Scheme 1.15).

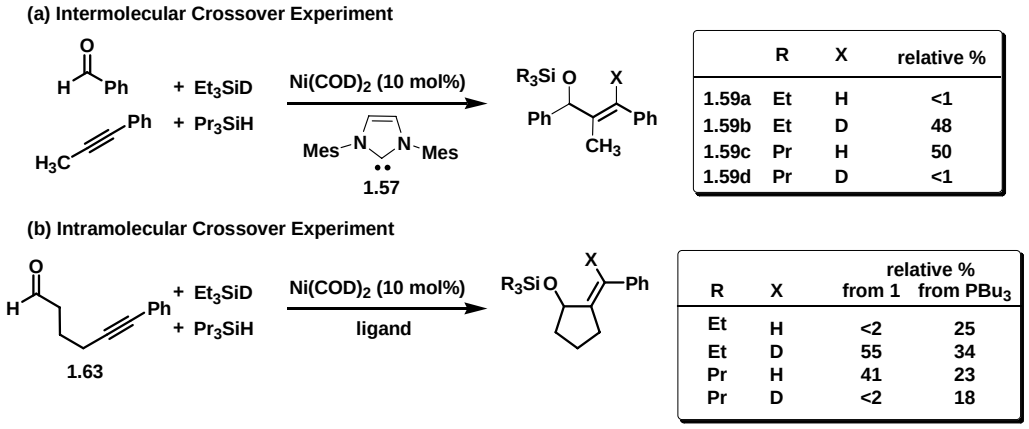


Scheme 1.15 Ni-catalyzed reductive coupling of alkynes, aldehydes, and organosilanes.

A particularly intriguing feature of these studies is the significant difference in scope of catalysts derived from PBu_3 and the imidazolium carbene ligand. Accordingly, they examined crossover experiments between Et_3SiD and Pr_3SiH to gain insight into a mechanistic probe. With $Ni(COD)_2$ and carbene ligand complex, non-crossover products **1.59b** and **1.59c** were produced in comparable amounts, and < 1% of crossover products was observed (Scheme 1.16 (a)). In addition, the crossover experiment was applied to the

intramolecular reductive coupling of an ynal **1.63**.[33] In case of $Ni(COD)_2$ with a carbene ligand, the results were very similar to those of intermolecular reductive coupling. However, significant crossover was observed in the case of $Ni(COD)_2$ with PBu_3 (Scheme 1.16 (b)).

Table 1.3 Inter- and intramolecular crossover experiments.

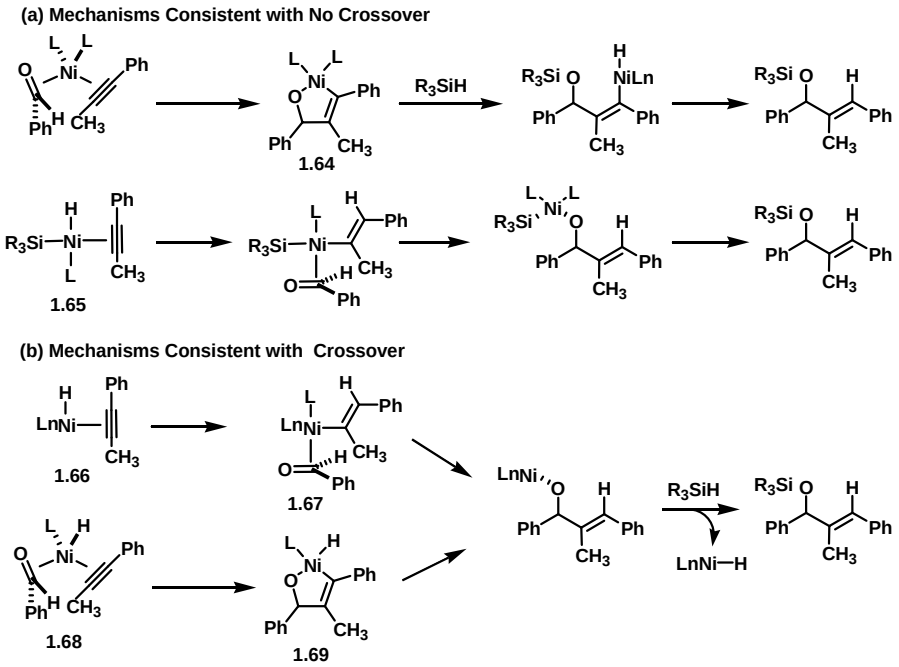


	R	X	relative %
1.59a	Et	H	<1
1.59b	Et	D	48
1.59c	Pr	H	50
1.59d	Pr	D	<1

R	X	relative % from 1	relative % from PBu_3
Et	H	<2	25
Et	D	55	34
Pr	H	41	23
Pr	D	<2	18

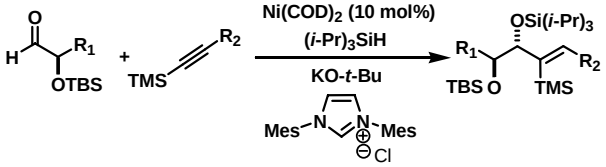
Based on the crossover experiment results, the author suggested the mechanisms of the two catalyst systems are fundamentally different. The author proposed two possible mechanisms for $Ni(COD)_2$ and carbene ligand system which are consistent with the lack of crossover. The first scenario is the formation of metallacycle **1.64** *via* oxidative coupling followed by a σ-bond metathesis with silane. The second scenario involves a nickel hydride species **1.65** (Scheme 1.16 (a)). However, the extensive crossover observed in the reductive cyclization catalyzed by $Ni(COD)_2/Bu_3P$ is clearly inconsistent with either of the aforementioned mechanisms. In order to explain the observed extensive crossover, the author proposed two other possible mechanisms. The first mechanism includes the formation of nickel hydride species **1.66** which undergoes sequential alkyne and aldehyde insertions *via* intermediate **1.67** which would lead to

crossover. Alternatively, a nickel hydride species **1.68** mediates oxidative coupling in the formation of metallacycle **1.69** which would also lead to crossover (Scheme 1.16(b)).



Scheme 1.16 Possible mechanisms.

The Montgomery group extended the Ni catalyzed reductive coupling of alkynes and aldehydes to the intermolecular diastereoslective coupling of alkynes and α-silyloxy-aldehydes.[34] Optimal conditions were found utilizing $(i\text{-Pr})_3SiH$ as the reducing agent, TBS as the α-hydroxy protection group on the aldehyde, and trimethylsilyl alkynes at room temperature. Under optimized conditions, both aliphatic and aromatic alkynyl silanes smoothly underwent reductive coupling to afford the *anti*-1,2-diols in high yields and good diastereoselectivities (Scheme 1.17).

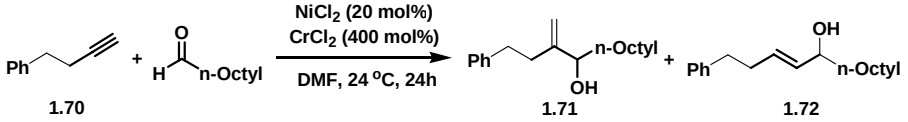


entry	R_1	R_2	dr (anti:syn)	yield(%)
1	CH_3	CH_3	88:12	81
2	CH_3	Ph	89:11	75
3	n-pnetyl	CH_3	>98:2	85
4	n-pentyl	Ph	>98:2	80

Scheme 1.17 Reductive coupling of alkynes and α-silyloxyaldehydes.

1.3.3 Ni-Cr System

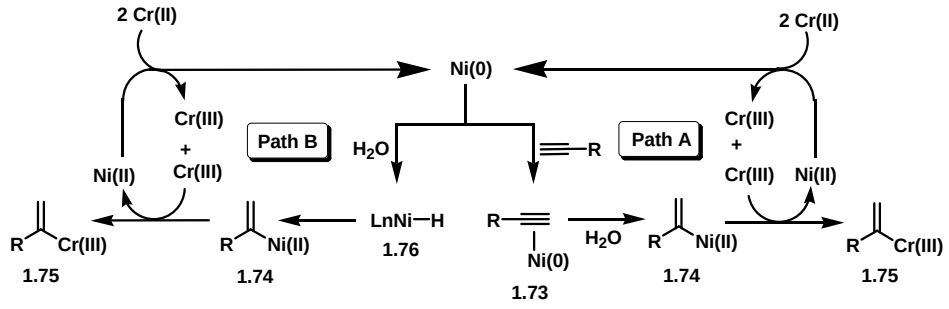
It is well known that 3-alkyl-substituted allylic alcohols can be prepared *via* hydrometallation methods[24] or Ni-catalyzed intermolecular reductive couplings.[26,32] However, it is not easy to prepare 2-alkyl-substituted allylic alcohols from a terminal alkyne and an aldehyde. In 2003, the Takai group reported Ni-catalyzed regioselective coupling of terminal alkynes and aldehydes leading to 2-alkyl-substituted allylic alcohol products.[35] Upon exposure of an aldehyde to terminal alkyne **1.70** in the presence of excess $CrCl_2$, catalytic $NiCl_2$, catalytic PPh_3, and H_2O in DMF, a mixture of the two allylic alcohols **1.71** and **1.72** was obtained in 78% yield. The 2-alkyl-substituted allylic alcohol **1.71** was produced selectively. The key to the success of these reactions is the addition of a small amount of water to the reaction mixture. It was also found that the addition of triphenylphosphine to the reaction was necessary to stabilize the nickel catalyst during the course of the reaction (Scheme 1.18).[35a]



entry	additive	1.71	1.72
1	H_2O	trace	trace
2	H_2O, PPh_3	71%	7%

Scheme 1.18 Regioselective reductive coupling of alkynes and aldehydes.

Two possible reaction pathways were proposed for the formation of the alkenyl nickel intermediate **1.74** from terminal alkynes. In **Path A**, the coordination of a terminal alkyne to Ni(0) generated by the reduction of nickel(II) with 2 equiv. of chromium (II) produces a nickel-alkyne complex **1.73.** A reaction of the complex **1.73** with water gives the alkenylnickel species **1.74**, which transmetallates to afford alkenylchromium reagent **1.75**. In **Path B**, nickel(0) reacts immediately with water to give a nickel-hydride species **1.76.** Insertion of the nickel-hydride species into the terminal alkyne gives the alkenylnickel species **1.74** (Scheme 1.19).

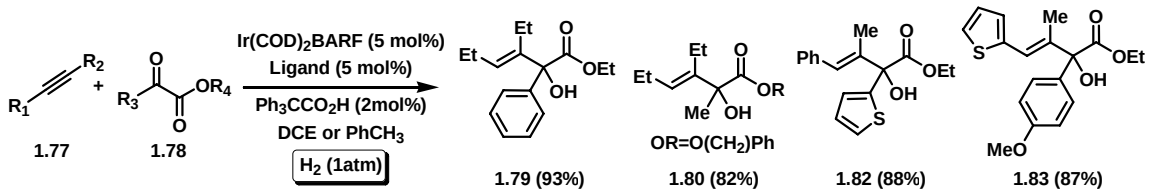


Scheme 1.19 Proposed catalytic cycles.

1.3.4 Ir-H_2 System

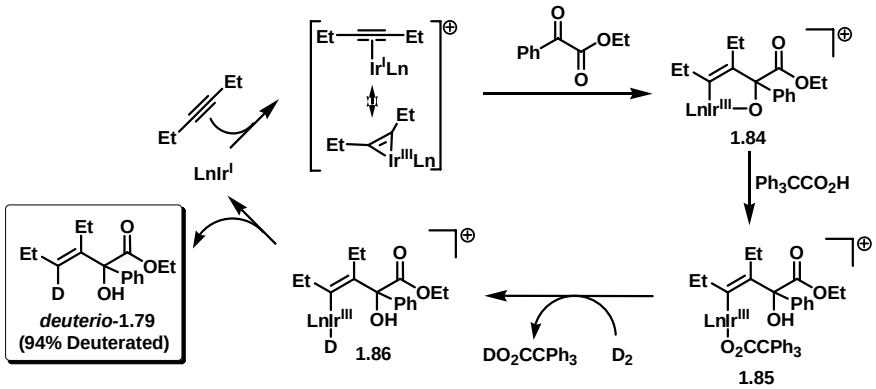
The Krische group has developed the reductive couplings of conjugated dienes[36], enynes,[37] and diynes[38] to carbonyl partners using a cationic rhodium catalyst under hydrogenation conditions. However, under the conditions of rhodium catalysis, simple nonconjugated alkyl substituted alkynes fail to react. In order to overcome this limitation, the group assayed cationic iridium complexes. Upon exposure of alkyne **1.77** to α-ketoester **1.78** under 1 atm of hydrogen in the presence of $Ir(COD)_2BARF$, DPPF, and triphenylacetic acid, α-hydroxyesters **1.79-1.83** were obtained in excellent yields as a single alkene geometrical isomer. The nonsymmetric alkyl-substituted alkynes coupled

regioselectively proximal to the methyl terminus to produce the corresponding products **1.82** and **1.83** in excellent yields. Furthermore, regioselectivity and olefin geometry are completely controlled (Scheme 1.20).[39]



Scheme 1.20 Ir-catalyzed reductive coupling of alkynes and carbonyls.

The author proposed a possible mechanism based on the deuterium-labeling study and the regioselectivity analysis. Alkyne-carbonyl oxidative coupling would furnish an oxametallacyclic intermediate **1.84**, which undergoes protonolytic cleavage by the Brønsted acid co-catalyst to produce a cationic iridium carboxylate **1.85**. Hydrogenolysis of the Ir-O bond followed by C-D reductive elimination of **1.86** would deliver *deuterio*-**1.79** along with the starting cationic iridium complex to close the catalytic cycle (Scheme 1.21).



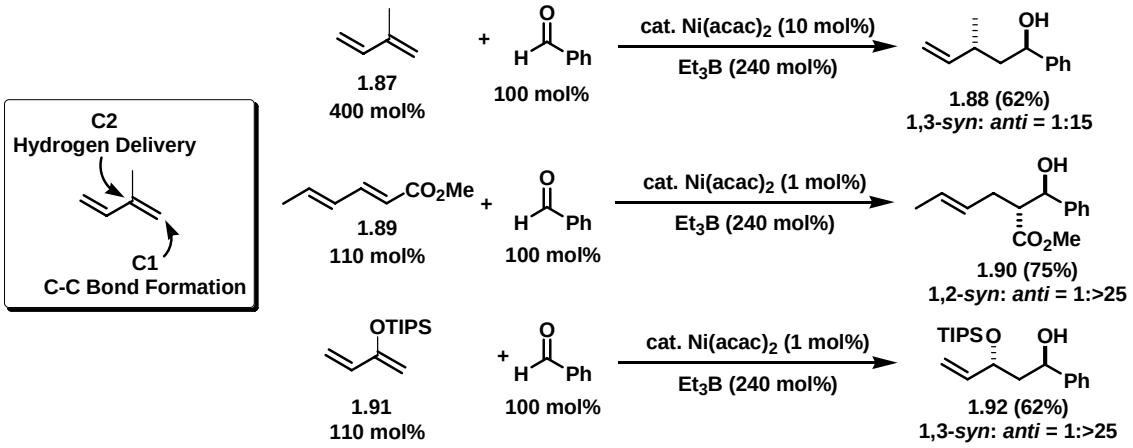
Scheme 1.21 Plausible catalytic cycle as supported by ^{2}H-labeling.

1.4 REDUCTIVE COUPLING OF 1,3-DIENES WITH CARBONYLS

Homoallylation of carbonyl compounds is an important carbon-carbon bond forming reaction for the preparation of bishomollylic alcohols. However, this process has received little attention, presumably due to the limited homoallylating agents and the low nucleophilicity of homoallylic transition metal species. Recently, metal catalyzed intermolecular reductive homoallylations have received increasing attention as an efficient homoallylation method to avoid using stoichiometric homoallylating reagents.

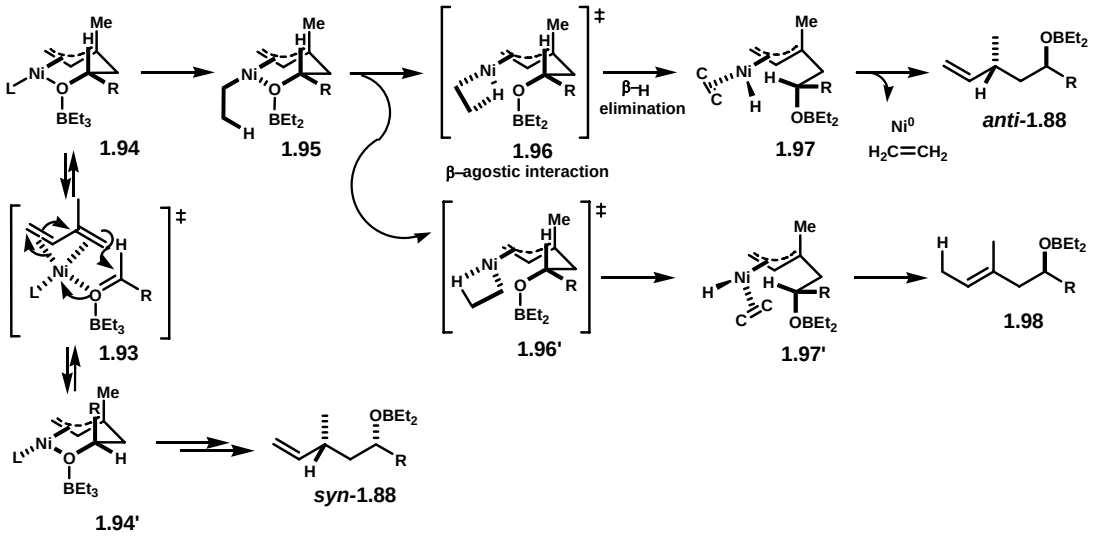
1.4.1 Ni-Borane System

In 1998, the Tamaru group reported the highly regio- and stereoselective Ni-catalyzed reductive homoallylation of 1,3-dienes and aldehydes.[40] It was found that $Ni(acac)_2$ combined with triethylborane catalyzed the homoallylation of benzaldehyde with 1,3-dienes (**1.87, 1.89,** and **1.91**) to provide bishomoallylic alcohols (**1.88**, **1.90**, and **1.92**) in excellent yields and with high regio- and stereoselectivities (Scheme 1.22).[40a] The reaction is remarkable in many respects. First, carbon-carbon bond formation only occurred at the C1 position of the diene moiety with an exclusive delivery of hydrogen at C2 position. Second, the reaction exhibits high 1,2- and 1,3-diastereoselectivity providing 1,2-*anti*-products (from *E*-1,3-diene) and 1,3-*anti*-products. Economically, the low cost of the reagents [$Ni(acac)_2$ and Et_3B] and a 1:1 stoichiometry of the reaction partners (diene and benzaldehyde) are quite attractive. It is noteworthy to add that for the first time, Et_3B played an important role as a reducing agent in maintaining the catalytic cycle for transition-metal-catalyzed reductive coupling reaction.



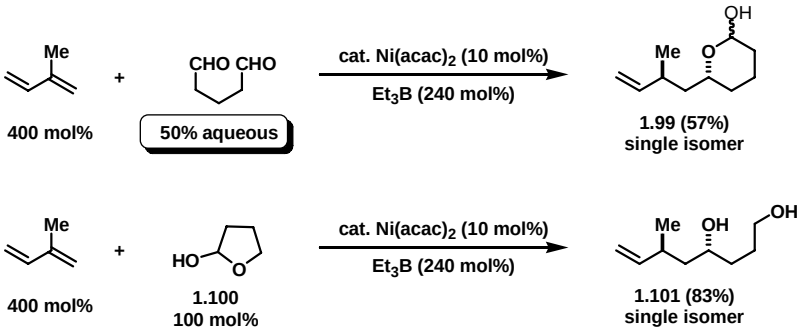
Scheme 1.22 Ni-catalyzed homoallylation of benzaldehyde with dienes.

The author proposed the most plausible reaction pathway that accommodates both stereoselectivity leading to 1,3-*anti*-product over 1,3-*syn*-product and regioselectivity which gives homoallylation products over the allylation products where isoprene is representative of dienes. The regioselectivity of dienes (reacting either at C1 or C4 with an aldehyde) might be predominantly controlled by the electron densities on the diene termini, and the reaction occurs at the termini bearing the highest electron density. The 1,3-*anti*-diastereoselectivity might be explained by the relative stability of the two intermediates **1.94** and **1.94'**. Since intermediate **1.94'** suffers from 1,3-diaxial repulsion between an aldehyde R group and isoprene methyl group, the reaction should proceed selectively through intermediate **1.94**. Moreover, the route leading to intermediate **1.97** is expected to be favored over the one leading to intermediate **1.97'** since the β-agostic interaction of the Et group with the vacant site on Ni, *cis* to the Et group. This vacant site can be created by dissociation of an oxygen ligand. (Scheme 1.23).[40c]



Scheme 1.23 Plausible reaction pathways selectively leading to 1,3-*anti*-product.

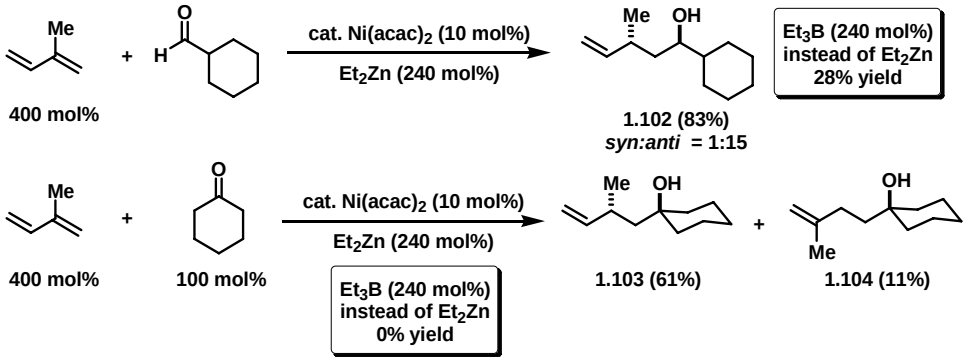
Generally, reactions with homoallylic metals (e.g. Li, Mg) should be performed with care under anhydrous conditions, and are generally not effective with acidic compounds. In 2001, the Tamaru group found that the Ni-catalyzed reductive coupling of dienes and aldehydes could be performed in the presence of water and alcohols.[41] Isoprene reacted with glutaraldehyde (available as a 50% aqueous solution) regioselectively at the C1 position and stereoselectively to furnish 1,3-*anti*-product **1.99** in 57% yield as a single isomer. Hemiacetal **1.100** also participated in this reaction to produce the coupling product **1.101** in 83% yield as a single isomer (Scheme 1.24).



Scheme 1.24 Ni-catalyzed homoallylation in the presence of water and hemiacetal.

1.4.2 Ni-Zn System

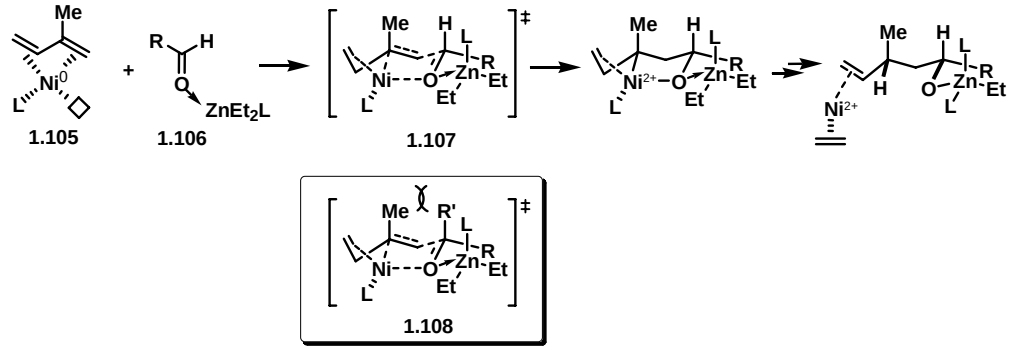
In 1999, the Tamaru group developed a Ni/Et_2Zn system for the reductive homoallylation reaction. The Ni/Et_2Zn combination is particularly effective for the homoallylation of saturated aldehydes and ketones, which were unreactive with the Ni/Et_3B system. Treatment of cyclohexane carboxaldehyde with excess isoprene in the presence of a catalytic amount of $Ni(acac)_2$ and 2.4 equiv. of Et_2Zn generated the coupling product **1.102** in 83% yield with good 1,3-*anti*-selectivity. Ketones were entirely unreactive with the Ni/BEt_3 catalyst system. However, the Ni/Et_2Zn system proved to be advantageous for reactions with ketones. In the reaction with ketones, partial loss of regioselectivity was observed and mixtures of **1.103** (the C1 addition product) and **1.104** (the C4 addition product) were obtained in a ratio of 6:1 (Scheme 1.25).[42]



Scheme 1.25: Ni-catalyzed homoallylation of aldehydes and ketones.

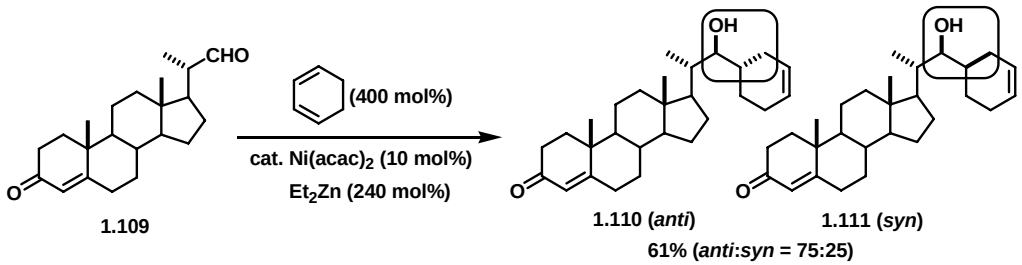
The proposed mechanism for the homoallylation of aldehydes with the Ni/Et_2Zn is illustrated in Scheme 1.26. The *s-trans*-isoprenenickel(0) complex **1.105** selectively reacts at the C1 position bearing the highest electron density, and the carbonyl group of the aldehyde is activated by Et_2Zn *via* **1.106**. In the transition state **1.107**, the aldehyde may be arranged in such a way to avoid a quasi-1,3-diaxial repulsion to furnish the 1,3-

anti-product. With a ketone however, a 1,3-diaxial repulsion is inevitable in transition state **1.108**. As a result, a sterically less demanding C4 addition of isoprene may compete with C1 addition to give a mixture of **1.103** and **1.104**.



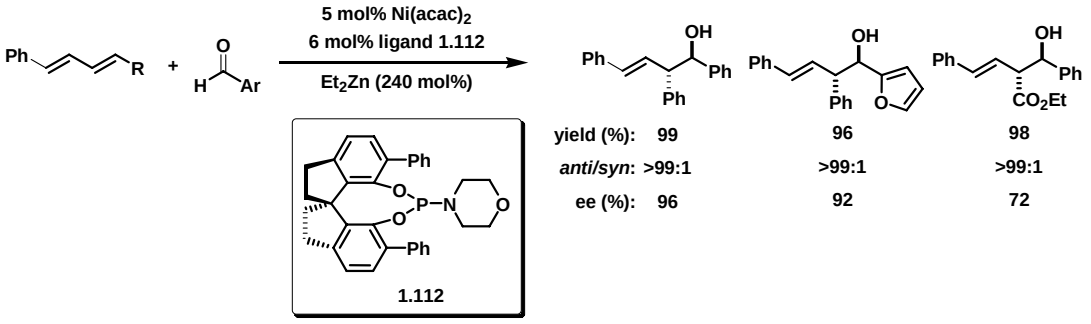
Scheme 1.26 Proposed transition state models.

In 2002, the Loh group reported Ni-catalyzed homoallylation of cyclic diene (1,3-cyclohexadiene) and aldehydes in the presence of Et_2Zn as the reducing reagent. 1,3-Cyclohexadiene reacted with the chiral steroidal aldehyde **1.109** to afford the desired product **1.110** and **1.111** in 61% combined yield and a moderate 3:1 1,2-diastereoselectivity. The author proposed that a less rigid, open-chain transition state may be responsible for the low 1,2-diastereoselectivity observed with the cyclic diene (Scheme 1.27).[43]



Scheme 1.27 Ni-catalyzed homoallylation of aldehydes with cyclic 1,3-dienes.

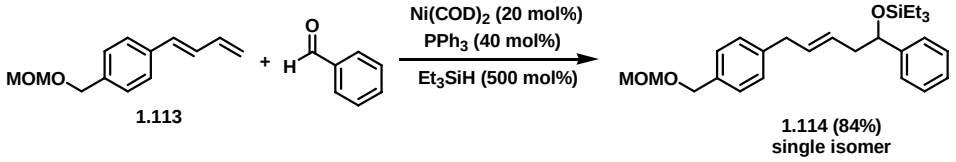
In 2007, the Zhou group reported the first asymmetric reductive coupling of 1,3-dienes and aldehydes. To achieve high enantioselectivity, the group examined nickel complexes ligated with bulky spirobiindane phosphoramidite ligands, and employed Et_2Zn as a reducing reagent. With ligand **1.112**, enantiomerically enriched bishomoallylic alcohols were produced in high yields with excellent diastereoselectivities and enantioselectivities (Scheme 1.28).[44]



Scheme 1.28 Asymmetric reductive coupling of 1,3-dienes and aldehydes.

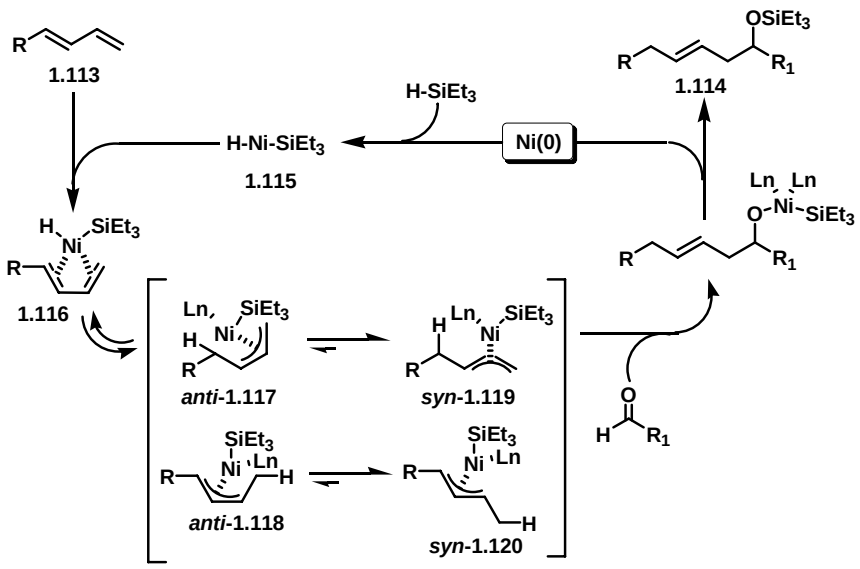
1.4.3 Ni-Silane System

In 1998, the Mori group introduced the $Ni(COD)_2/PPh_3/Et_3SiH$ catalyst system for intermolecular reductive coupling of 1,3-dienes and aldehyde. Upon exposure of diene **1.113** to benzaldehyde in the presence of $Ni(COD)_2$, PPh_3, and Et_3SiH in toluene at 50 ^oC, triethylsilyl protected alcohol **1.114** was obtained in 84% yield as sole product in a regio- and stereoselective manner (Scheme 1.29).[45]



Scheme 1.29 Ni-Catalyzed homoallylation of aldehydes with organosilane.

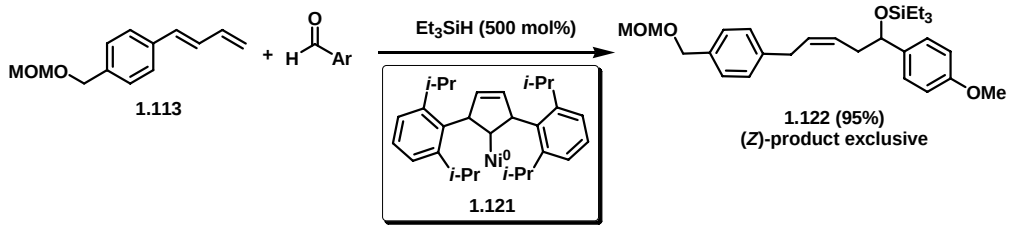
The proposed reaction pathways are outlined in Scheme 1.30. In this reaction, nickel hydride complex **1.115** generated by the oxidative addition of Et_3SiH to Ni(0) is coordinated by diene **1.113** to give complex **1.116**. The insertion of the diene into the nickel-hydride bond produces nickel π-allyl complexes *anti*-**1.117** and *anti*-**1.118**, which would be in equilibrium with the more stable *syn*-**1.119** and *syn*-**1.120**. Then, *syn*-**1.119** intermediate reacts with an aldehyde at the less substituted terminal carbon to give silyl-protected *E*-**1.114**.



Scheme 1.30 Proposed reaction pathways.

The Mori group also developed a Ni/carbene/Et_3SiH catalyst system for the reductive coupling of 1,3-dienes and aldehydes.[46] It was found that Ni-carbene complex **1.121** showed a unique property in the ability to couple 1,3-dienes and aldehydes to afford coupling product **1.122**, possessing the (*Z*)-olefin exclusively in good yield in a highly stereoselective manner (Scheme 1.31).[45] This indicates that the reactivity of Ni-

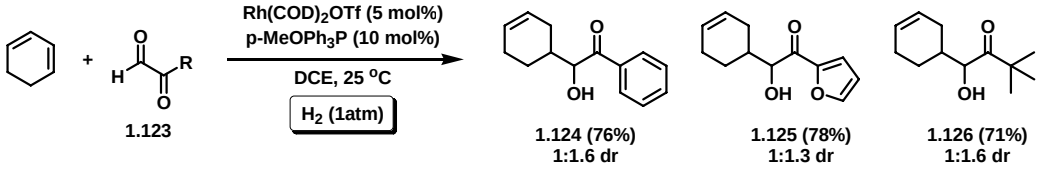
carbene complex **1.121** is quite different from those of the traditional Ni(0)-phosphine ligated systems which selectively produce (*E*)-olefin products.[45]



Scheme 1.31 Ni-catalyzed homoallylation of aldehydes with a carbene ligand.

1.4.4 Rh-H_2 System

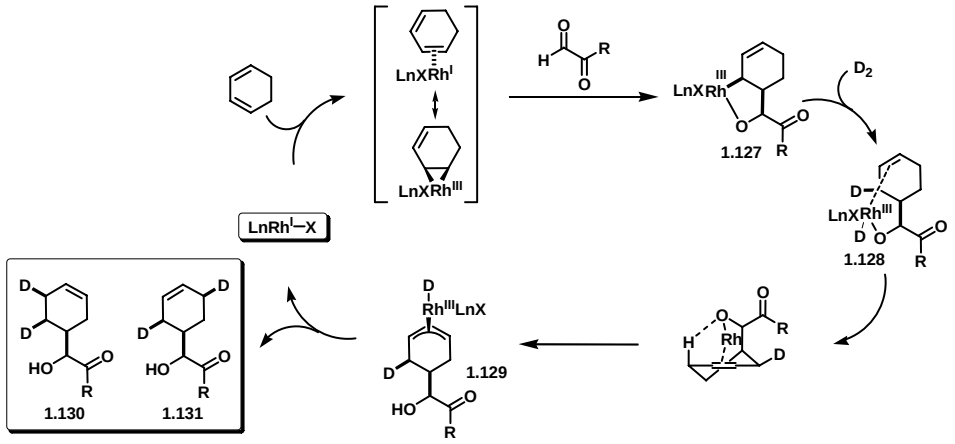
In 2003, the Krische group reported the rhodium-catalyzed reductive coupling of cyclohexadiene and carbonyls under hydrogenation conditions. It is noteworthy that hydrogenation of conjugated alkenes in the presence of phenyl glyoxal provided reductive carbonyl-ene type coupling products. Under optimum conditions, 1,3-cyclohexadiene coupled to a range of α-ketoaldehydes **1.123** to produce the corresponding products (**1.124-1.126**) in good yields (Scheme 1.32).[37a]



Scheme 1.32 Rh-catalyzed reductive coupling of 1,3-dienes and carbonyls.

Based on a deuterium labeling study, a plausible mechanism was proposed. Initial oxidative coupling of diene and glyoxal would furnish an oxarhodacyle **1.127**, which then reacts with deuterium *via* σ-bond metathesis to afford rhodium alkoxide complex **1.128**. Subsequent abstraction of an allylic hydrogen provides a rhodium π-allyl complex **1.129**,

which upon C-D reductive elimination delivers the dideuterated products as an equimolar distribution of regioisomers **1.130** and **1.131** (Scheme 1.33).



Scheme 1.33 Plausible catalytic cycle supported by ^{2}H-labeling.

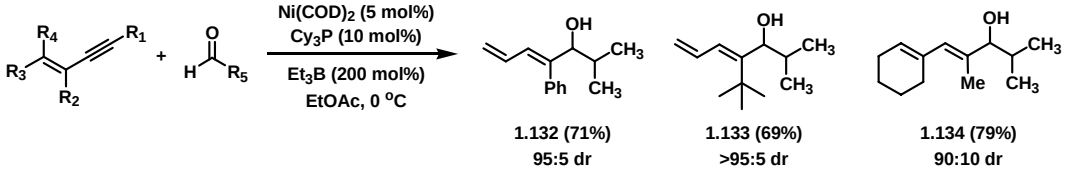
1.5 REDUCTIVE COUPLING OF CONJUGATED ALKYNES WITH CARBONYLS

1,3-Dienes are important and useful intermediates in synthetic chemistry. Since they can be used in an array of cycloaddition reactions such as Diels-Alder reaction, there are a variety of efficient methods for their preparation.[47] Recently, a new method for the synthesis of 1,3-dienes via metal-catalyzed reductive coupling of 1,3-enyne and carbonyl compounds has been developed by several groups.[32, 37, 48]

1.5.1 Ni-Borane System

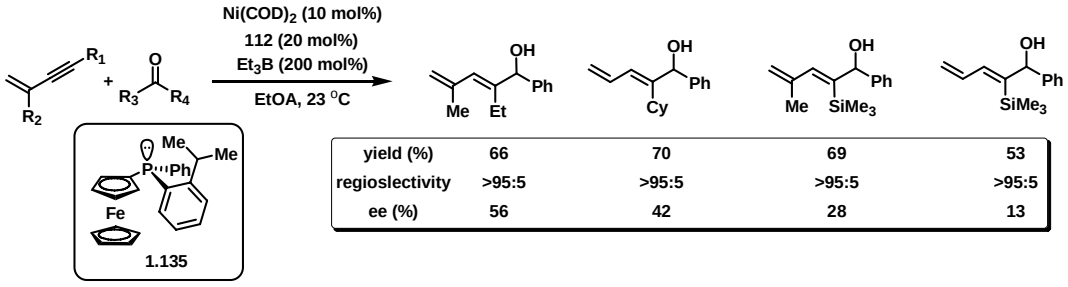
In 2004, the Jamison group reported the Ni-catalyzed reductive coupling of 1,3-enynes and aldehydes to produce 1,3-diene compounds. In the nickel catalyzed coupling reaction of aryl alkyl acetylene (Ar-C≡C-alkyl), the regioselectivity is generally very high (>95:5), favoring carbon-carbon bond formation distal to the aromatic group. Interestingly, electronically similar and smaller vinyl groups cause a complete reversal in

sense of regioselectivity. In these cases, carbon-carbon bond formation proximal to the aryl substituent (**1.132**) is favored. Additionally, the alkene substituent provided a remarkable increase in reactivity. For instance, sterically demanding *t*-Bu-C≡C-CH=CH_2 underwent reductive coupling, favoring carbon-carbon bond formation adjacent to the *tert*-Bu group (**1.133**). It is important to note that the directing ability of the alkene depends neither on the nature or size of the other alkyne substitution (aryl, akyl (1^o, 2^o, 3^o)) nor on the degree of alkene substituent (**1.134**) (Scheme 1.34).[48a]



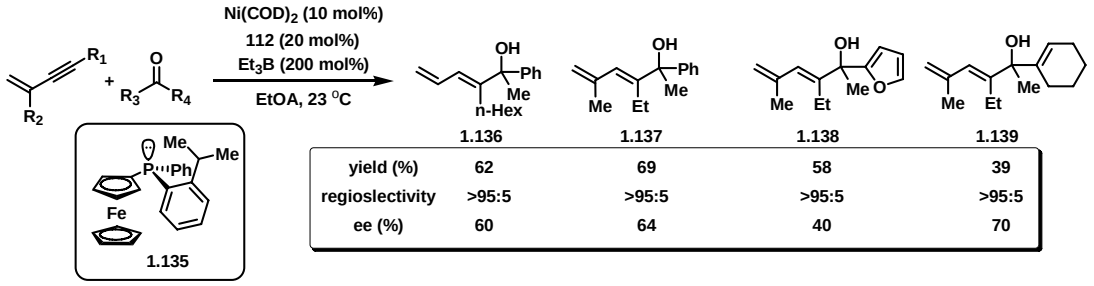
Scheme 1.34 Ni-Catalyzed reductive coupling of 1,3-enynes and aldehydes.

The Jamison group also developed an enantioselective variant of nickel-catalyzed reductive coupling of 1,3-enynes and aldehydes by employing *P*-chiral ferrocenyl mono-phosphine ligand. Among monodentate phosphine ligands assayed, ferrocenylphosphine **1.135** provided high levels of regioselectivity (>95:5) with moderate enantioselectivities (Scheme 1.35).[48b]



Scheme 1.35 Asymmetric reductive coupling of 1,3-enynes with aldehydes.

The Jamison group extended this reaction to the asymmetric reductive coupling of 1,3-enynes with ketones. The catalytic reductive coupling of alkyl 1,3-enynes with acetophenone produced the tertiary alcohol product **1.136** in 62% yield with excellent regioselectivity. In addition, the reaction of commercially available 2-methyl-1-hexene-3-yne with acetophenone gave coupling product **1.137** in good yield with complete regiocontrol. In addition to acetophenone, a heteroaromatic ketone and a α,β-unsaturated ketone successfully participated in the reaction to give the corresponding coupling products **1.138** and **1.139** in good yields and with good enantioselectivities (Scheme 1.36).[48c]



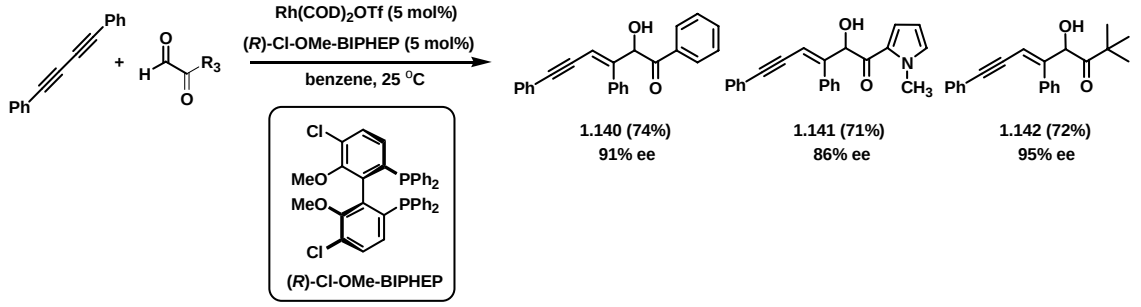
	1.136	1.137	1.138	1.139
yield (%)	62	69	58	39
regioslectivity	>95:5	>95:5	>95:5	>95:5
ee (%)	60	64	40	70

Scheme 1.36 Asymmetric reductive coupling of 1,3-enynes with ketones.

1.5.2 Rh-H_2 System

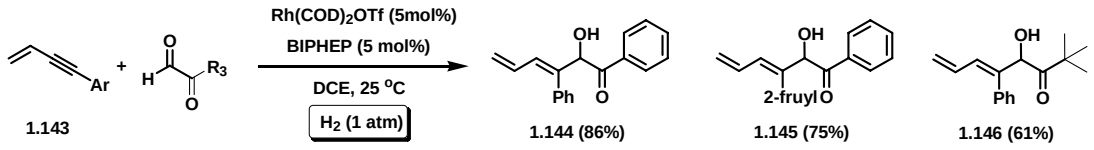
In 2003, the Krische group reported the rhodium-catalyzed reductive coupling of diynes and activated aldehydes under hydrogenation conditions.[38] Treatment of diphenylbutadiyne with phenyl glyoxal and catalytic $[Rh(COD)_2]OTf$ in dichloroethane afforded the conjugated diene product **1.140** in good yield as a single regio- and stereoisomer. To explore the feasibility of an enantioselective variant, a variety of commercially available chiral triarylphosphine ligands were screened. Among those assayed, (*R*)-Cl-MeO-BIPHEP proved superior, providing **1.140** in 74% yield and 76%

ee. Through variation of the reaction medium, benzene was identified as the ideal solvent, affording a 74% yield of **1.140** in 91% ee. Heteroaryl glyoxal and alkyl glyoxal also participated in the reaction to produce the corresponding products **1.141** and **1.142** in 86% ee and 95% ee, respectively (Scheme 1.37).[38a]



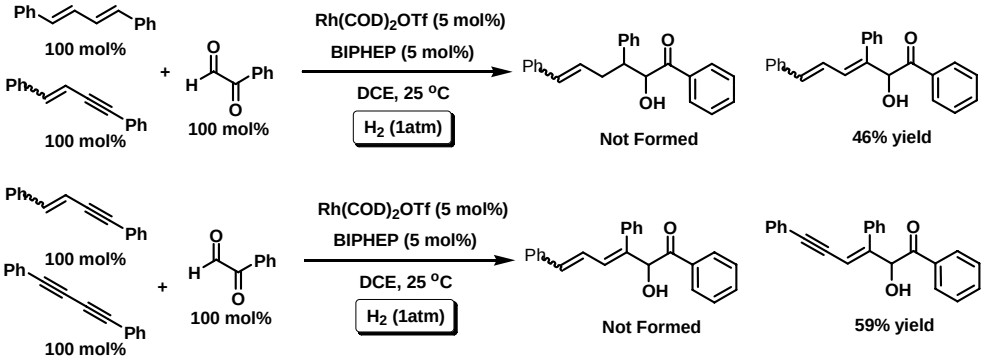
Scheme 1.37 Asymmetric reductive coupling under hydrogenation conditions.

The reductive coupling of 1,3-diynes and activated aldehydes was further extended to the reductive coupling of 1,3-enynes and α-ketoaldehydes. Exposure of 1-phenyl but-3-en-1-yne **1.143** to phenyl glyoxal in the presence of $Rh(COD)_2OTf$ and BIPHEP in DCE under an atmosphere of hydrogen provided the highly unsaturated diene-containing product **1.144** in 86% yield as a single regio- and stereoisomer. In addition, the reaction of heteroaryl and alkyl glyoxal gave the corresponding products **1.145** and **1.146** in good yields. Similar to Jamison's Ni-catalyzed reductive coupling of 1,3-enynes with carbonyls,[48] the regioselectivity is generally very high (>95:5), favoring carbon-carbon bond formation distal to the vinyl group. (Scheme 1.38).[37a]



Scheme 1.38 Rh-catalyzed reductive coupling of 1,3-enynes and carbonyls.

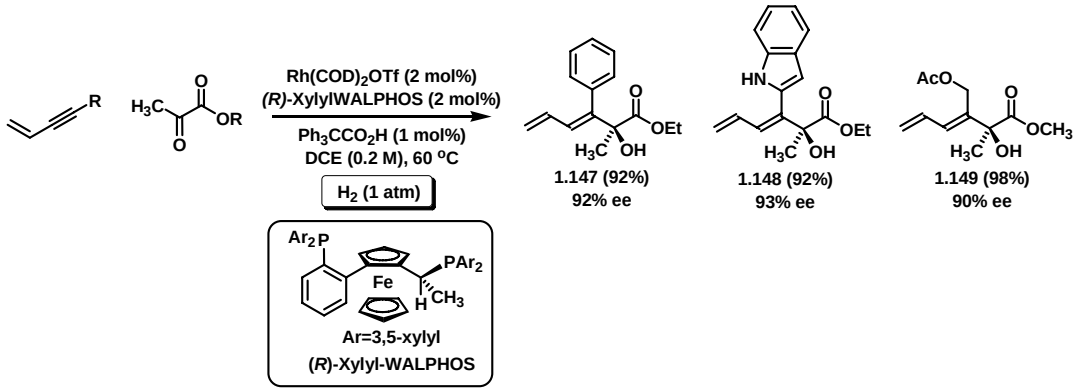
To gain insight into the origins of chemo- and regioselectivity observed for the intermolecular reductive coupling of 1,3-diynes and 1,3-enynes with α-ketoaldehydes, a series of competition experiments were performed. As a result, it was found that the diyne is the most reactive. Additionally, the enyne is more reactive than the diene for the reductive coupling reaction. Chemoselective coupling to the more highly unsaturated pronucleophile suggests preferential coordination of the most π-acidic reacting partner by low-valent rhodium and pronucleophile complexation to the metal center might control the chemoselectivity (Scheme 1.39).



Scheme 1.39 Competition experiments.

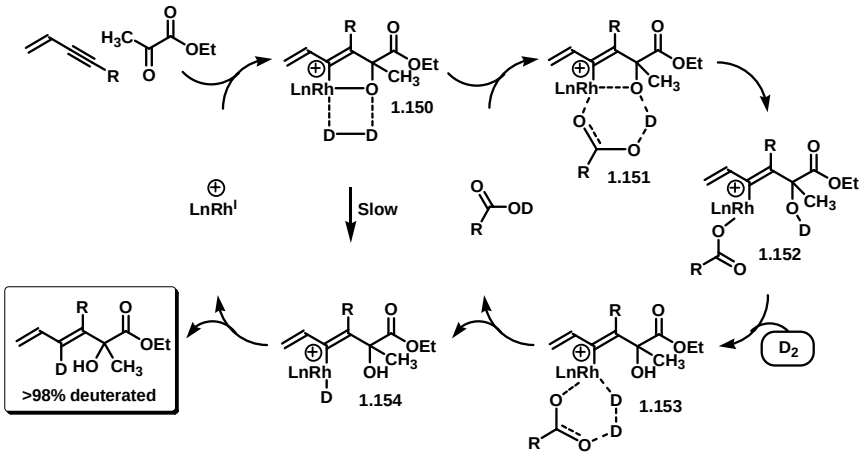
In 2006, the Krische group reported a Rh-catalyzed enantioselective reductive coupling of 1,3-enynes with pyruvates as a means of accessing enantiomerically enriched α-hydroxy acids. It was found that the reductive coupling of 1,3-phenylenyne with ethyl pyruvate in the presence of $Rh(COD)_2OTf$ and (*R*)-xylyl-WALPHOS produced the coupling product **1.147** in good enantiomeric excess but only moderate yield. It was thought that hydrogenolytic cleavage of the Rh-O bond in the catalytic cycle might be the rate determining step. Indeed, it is known that the Rh-O bond is easily cleaved in presence of protic additives such as H_2O.[49] Additionally, computational studies suggest

that four-centered transition structures for hydrogenolysis of Rh-O bonds are higher in energy than those occurring by way of six-centered transition structures involving rhodium carboxylates.[50] It was hypothesized that an acid cocatalyst might enhance reaction rate, a variety of acids were screened. Gratefully, triphenylacetic acid dramatically influenced the rate of conversion without decreasing enantioselectivity. Under optimized reaction conditions, a variety of 1,3-enynes were tested. Aryl, heteroaryl, alkyl substituted 1,3-enynes coupled very well to give products **1.147**-**1.149** in excellent enantioselectivies (Scheme 1.40).[37b]



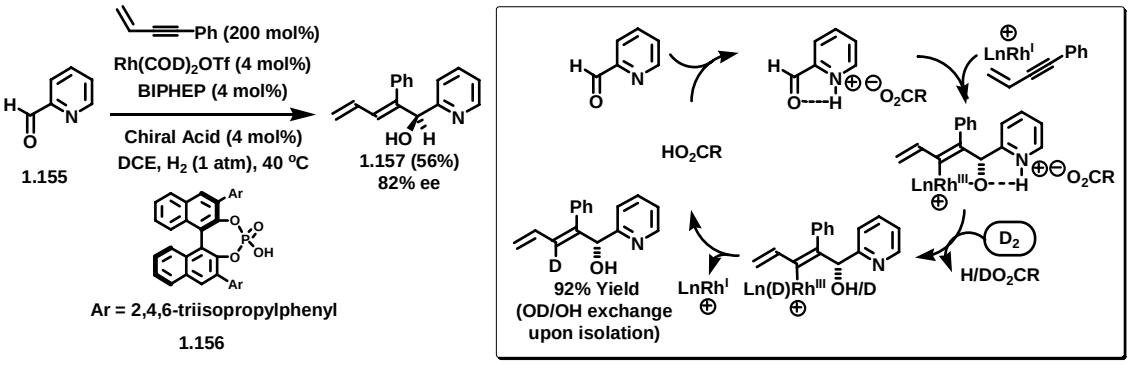
Scheme 1.40 Asymmetric reductive coupling of 1,3-enynes and activated ketones.

The results of the reductive coupling employing ac acid additive provided significant insight into the mechanistic framework of the rhodium-catalyzed reductive coupling of enynes and diynes. Based on the deuterium labeling study and acid additive effect, a plausible mechanism was proposed. The catalytic cycle is initiated by oxidative coupling of enyne and pyruvate to form oxarhodacyclopentene **1.150**. Subsequently, hydrolytic cleavage of Rh-O bond through **1.151** produces rhodium carboxylate **1.152.** Hydrogenolysis of Rh-O bond in **1.152** through six-centered transition structure **1.153** *via* σ-bond metathesis with deuterium gas generates alkenyl rhodium intermediate **1.154**, which undergoes C-H reductive elimination to close the catalytic cycle (Scheme 1.41).



Scheme 1.41 Proposed catalytic cycle.

Recently, the Krishce group disclosed a Rh-catalyzed reductive coupling of 1,3-enynes with heterocyclic aromatic aldehydes and ketones. In case of the reductive coupling of 1,3-phenyenyne to 2-pyridinecarboxaldehyde **1.155**, a chiral Brønsted acid co-catalyst **1.156**[51] derived from BINOL produced the optically enriched coupling product **1.157** in 82% ee. This result strongly suggests that carbon-carbon coupling is accelerated by substrate protonation *via* a LUMO lowering effect, and that the chiral acid co-catalyst is associated with 2-pyridine-carboxaldehyde during the enantiodeterming step (Scheme 1.42).[37c]



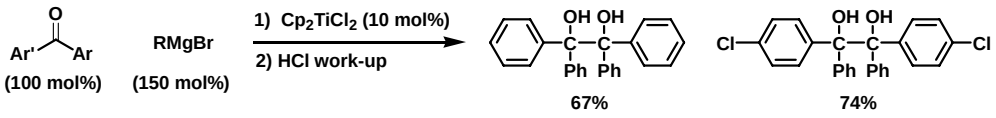
Scheme 1.42 Plausible catalytic mechanism as supported by chiral acid effect.

1.6 REDUCTIVE COUPLING OF CARBONYLS WITH CARBONYLS

Reductive coupling of carbonyl compounds have found extensive use in organic synthesis.[52] In particular, stereoselective pinacol couplings have received much attention since enantiomerically pure diols can be used for asymmetric syntheses.[53] In addition, the pinacol coupling has been employed as a key step in the syntheses of many natural products and pharmaceuticals.[54] In 1973, two research groups, Mukaiyama[55a] and Tyrilik,[55b] independently reported this coupling reaction mediated by metal. Later, in 1974, the McMurry group studied the pinacol coupling reaction in detail using either a $TiCl_3$-$LiAlH_4$ system or $TiCl_3$-Zn/Cu system.[55c] The importance of this reaction and the utility of the pinacol product warranted extensive studies employing other transition metals as reducing reagents in this coupling.

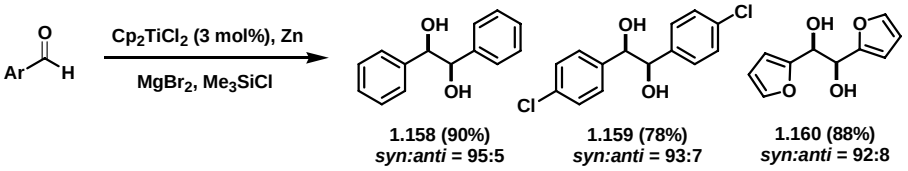
1.6.1 Titanium Catalysts

The Sato group reported that aliphatic aldehydes or ketones were reduced by Cp_2TiCl_2-catalyzed Grignard reagents to form the corresponding alcohols.[56] In the course of studying Ti-catalyzed reduction of aryl ketones, the Zhang group observed that when the reaction of Grinard reagents with diaryl ketones was carried out in the presence of a catalytic amount of Cp_2TiCl_2, reductive coupling was observed and usual 1,2-addition was suppressed. The author proposed that the principle intermediate of the catalytic reductive coupling could be [Cp_2TiH], and the unpaired electron on Ti is transferred to the ketones inducing some radical character at the ketone carbon atom (Scheme 1.43).[57]



Scheme 1.43 Ti-catalyzed pinacol coupling of diaryl ketones.

Later, highly diastereoselective Ti-catalyzed reductive coupling was developed by Gansäuer in 1997. To convert the known stoichiometric pinacol reaction[58] to a catalytic reaction, Gansäuer introduced Zn as a reductant and TMSCl as a promoter. The reductive coupling of benzaldehyde in the presence of Zn and Me_2SiCl_2 with 10 mol% of Cp_2TiCl_2 gave pinacol conversion to produce coupling product **1.158** in good yield but with low diastereoselectivity. The diastereoselectivity was improved by adding 1 equiv. of $MgBr_2$. It is believed that Mg would replace Zn to give a tighter dimeric titanium catalyst (Figure 1.2). 4-Chlorobenzaldehyde and 2-furanecarboxaldehyde participated in the reaction to give the corresponding pinacol products **1.159** and **1.160** in good yields with high diastereoselectivies (Scheme 1.44).[59]



Scheme 1.44 Pinacol coupling of aldehydes catalyzed by a titanocene complex.

Mechanistically, it was assumed that the catalytically active species could be a dimeric titanium complex binding both ketyl radicals. The observed *syn*-selectivity could be explained by minimization of steric interference through *anti*-orientation of the Ar groups in the complex **1.161**.

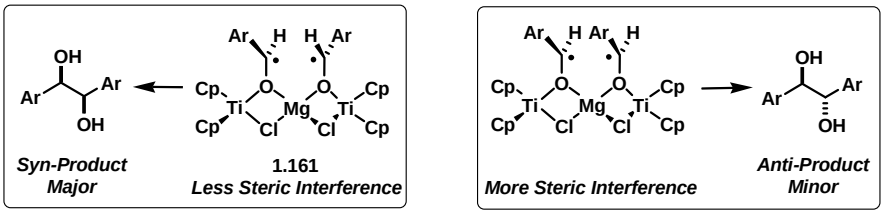
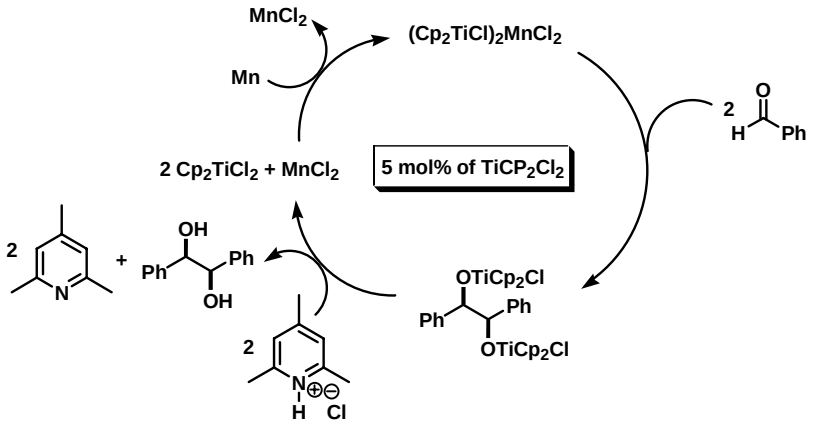


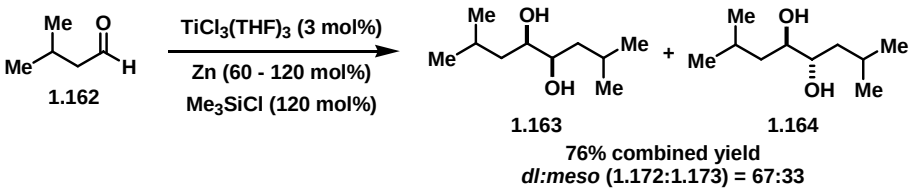
Figure 1.2 Catalytically active species controlling diastereoselectivity.

In 1998, the Gansäuer group demonstrated that catalytic turnover of titanium in the catalytic pinacol coupling could be achieved by protonation of a metal-oxygen bond in buffered protic media by properly adjusting the p*K*a of the employed acid additive. The use of 2,4,6-collidine hydrochloride (p*K*a value in water 7.43) as an acid additive improved both diastereoselectivity and reactivity in the Ti-catalyzed pinacol coupling. In addition, it was found that using manganese as a stoichiometric reductant in the coupling vastly superior to zinc in respect to both yield and diastereoselectivity. The proposed catalytic cycle is illustrated in Scheme 1.45.[60]



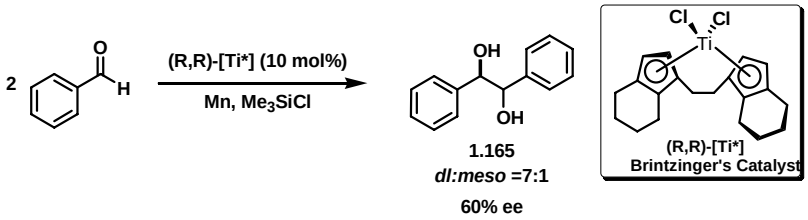
Scheme 1.45 Proposed catalytic cycle under protic conditions.

The Nelson group reported the use of organic-soluble Ti(III) complexes as highly efficient catalysts for pinacol homocoupling reactions. In the course of these studies, they discovered that the organic-soluble $TiCl_3(THF)_3$ was applicable to the pinacol coupling of enolization-prone aldehydes. Optimal conditions were determined to be reaction of the aldehyde with 1.2 equiv. of Zn, 1.2 equiv. of TMSCl, and 5 mol% of $TiCl_3(THF)_3$-*t*-BuOH. Alkyl aldehyde **1.162** was subjected to the reaction conditions to produce pinacol coupling products **1.163** and **1.164** in 76% yield with moderate diastereo-selectivity (Scheme 1.46).[61]



Scheme 1.46 Ti-catalyzed pinacol coupling of enolization-prone aldehydes.

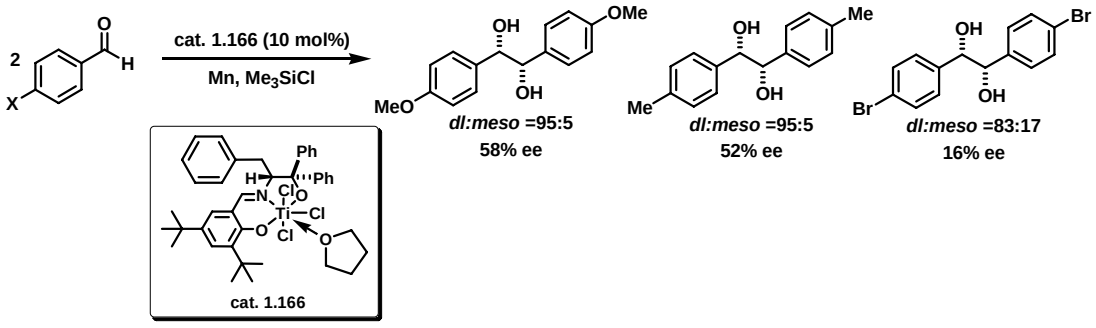
The Nicholas group reported the first titanium-catalyzed enantioselective pinacol coupling using chiral Brintzinger's catalyst, (*R,R*)-ethylenebis(tetrahydroindenyl)titanium dichloride. Under optimized conditions, the reductive homocoupling of benzaldehyde catalyzed by the chiral Ti-complex gave pinacol **1.165** in 60% ee. This result demonstrated the first catalytic asymmetric pinacol coupling and the viability of this approach to asymmetric synthesis of pinacols (Scheme 1.47).[62]



Scheme 1.47 Enantioselective pinacol coupling with Brintzinger's catatalyst.

In 2001, the Riant group reported a catalytic enantioselective pinacol coupling of aldehydes catalyzed by chiral titanium complexes. To achieve asymmetric induction, an air-stable, nonhygroscopic catalyst **1.166** derived from tridentate salen ligands and $TiCl_4$ was prepared and the feasibility of this catalyst for enantioselective pinacol coupling was investigated. A survey of various reductants indicated manganese to be the best choice at -10 ^{o}C. While electron-donating substituents gave a noticeable increase in the ee of the pinacol products (4-methoxybenzaldehyde and 4-methyl-benzaldehyde), the introduction

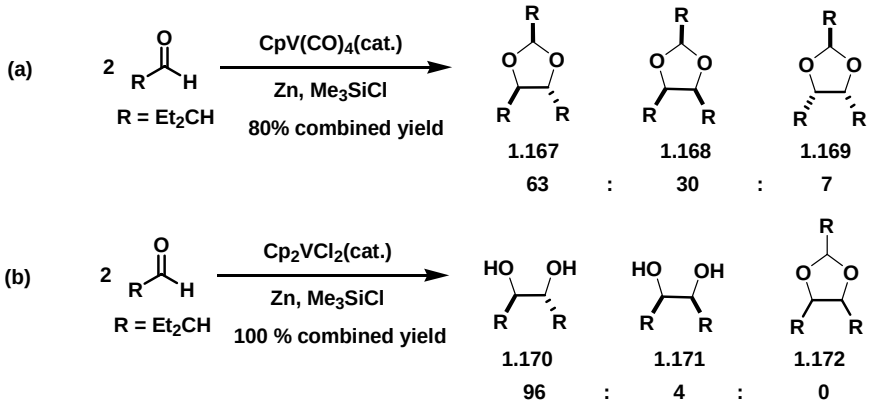
of an electron-withdrawing group strikingly decreased enantioselectivity (4-bromo-benzaldehyde) (Scheme 1.48).[63]



Scheme 1.48 Enantioselective Pinacol coupling by the Riant group.

1.6.2 Vanadium Catalysts

In 1996, the Hirao group reported the first vanadium-catalyzed reductive coupling of aldehydes. Treatment of hexanal with a catalytic amount of $CpV(CO)_4$ in the presence of zinc powder and chlorotrimethylsilane in DME at room temperature led to high yields of 2,4,5-tripentyl-1,3-dioxolanes **1.167**-**1.169** *via* the reductive coupling and acetalization of the 1,2-diol derivative (Scheme 1.49 (a)).[64a] Later, the group found that use of THF as solvent and Cp_2VCl_2 as catalyst led to the highly diastereoselective formation of the *dl*-1,2-diols **1.170** and **1.171** from secondary aliphatic aldehydes without formation of any olefinic products and 1,3-dioxolane **1.172**. In particular, this catalyst system was applicable to the pinacol coupling of a variety of secondary aliphatic aldehydes to give the desired products in good to excellent yields and with high diastereoselectivities. However, the pinacol coupling of primary aliphatic aldehydes and ketones still suffered from low diastereoselectivities with this catalyst system (Scheme 1.49 (b)).[64b]

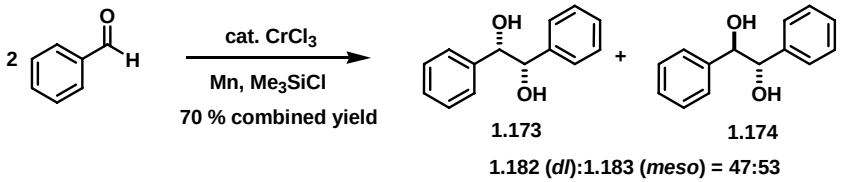


Scheme 1.49 Vanadium-catalyzed pinacol coupling of aliphatic aldehydes.

Recently, the catalytic pinacol coupling reaction in water was reported by the Hirao group.[65] It was demonstrated that the reaction successfully proceeded with VCl_3-Al catalyst system in water even in the absence of a chlorosilane, which was previously required as an essential additive in organic media. This catalyst system (VCl_3-Al-water) is considered to be of synthetic potential as an environmentally harmonious system.

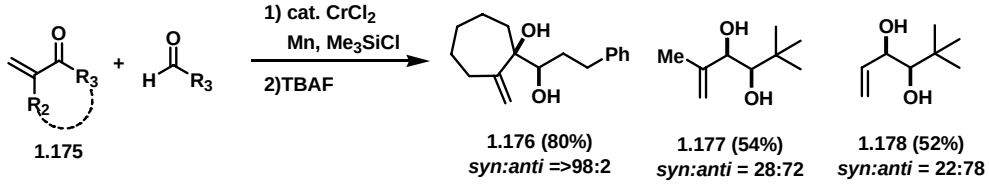
1.6.3 Chromium Catalysts

In the course of the study on chromium-catalyzed Nozaki-Hiyama-Kishi reaction, the Fürstner group observed that the use of electron deficient aldehydes afforded the pinacol as the major product.[66] Inspired by the Fürstner group's result, the Boland group systematically investigated the chromium-catalyzed reductive pinacol coupling of aromatic carbonyl compounds. Treatment of benzaldehyde in a binary solvent mixture of THF/DMF with $CrCl_3$ (5 mol%) and trimethylsilyl chloride in the presence of Mn-dust produced the reductive coupling products **1.173** and **1.174** in good yield (Scheme 1.50).[67]



Scheme 1.50 Cr-catalyzed reductive pinacol coupling of aromatic carbonyls.

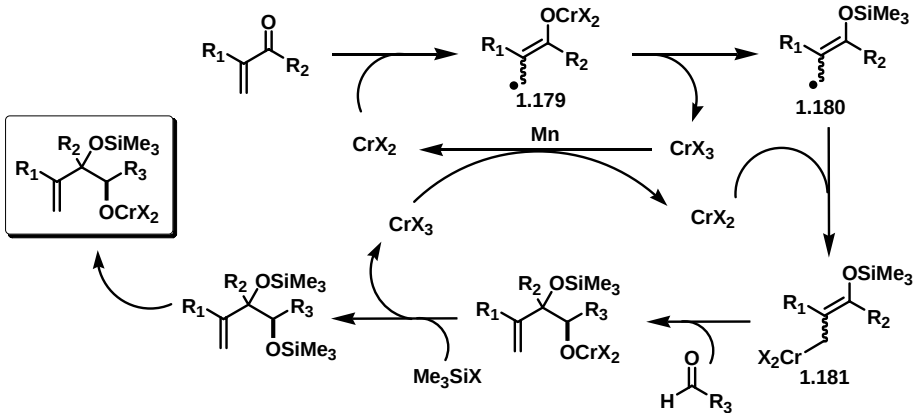
Most of catalytic pinacol coupling methods reported were limited to the homocoupling of aldehydes affording symmetrically substituted 1,2-diols. In 2001, the Takai group reported the cross pinacol-type coupling reaction between α,β-unsaturated carbonyl compounds and aldehydes using 4 equiv. of chromium(II) chloride.[68a] The catalytic variant of Takai's method was developed by Groth in 2002. They observed that the couplings of vinyl ketones **1.175** with aliphatic aldehydes proceed with only 10 mol% of chromium(II) chloride affording the desired products **1.176-1.178** in up to 80% yield and with up to >95% de (Scheme 1.51).[68b,68c]



Scheme 1.51 Cr-catalyzed diastereoselective pinacol-type cross coupling.

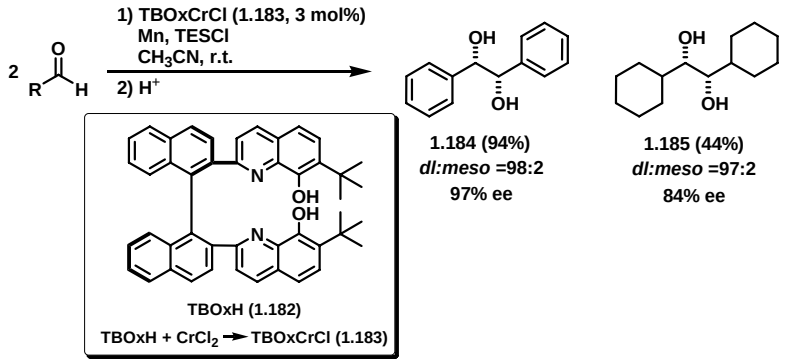
A postulated catalytic cycle is illustrated in Scheme 1.52 based on the mechanism of Takai.[68a] It should be noted that this reaction does not proceed through ketyl radicals. Instead, a nucleophilic attack of a chromium allyl apecies onto an aldehyde is proposed. The reduction of an α,β-unsaturated ketone with chromium(II) would generate the radical enolate **1.179**, which could be trapped with Me_3SiCl to give the allylic radical **1.180**. Such an allylic radical could be easily reduced with chromium(II) to afford the

corresponding allylic chromium species **1.181**. The coupling of allylic chromium complex **1.181** and the aldehyde led to 1,2-diols after the usual work-up.



Scheme 1.52 Postulated catalytic cycle.

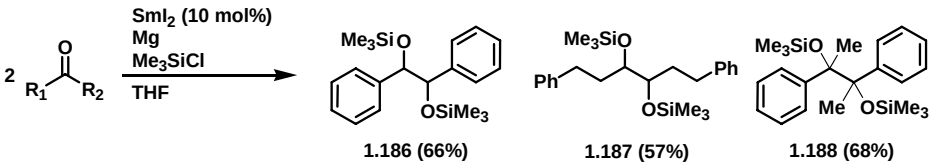
Highly enantioselective chromium-catalyzed pinacol couplings have been developed by the Yamamoto group using a new tethered bis(8-quinolinolato) ligand **1.182**. Treatment of benzaldehyde with co-reducing reagent (Mn), the product scavenger (TMSCl), and the precatalyst [TBSOxCr(III)Cl] **1.183** in CH_3CN under an atmosphere of argon at room temperature generated the pinacol coupling product **1.184** in 94% yield and 97% ee after acidic work-up. Additionally, the scope of this method was found not to be limited to aromatic aldehyde derivatives, as cyclohexanecarboxaldehyde underwent pinacolization (**1.185**, 44% yield, *dl*:*meso*=93:7, 84% ee). In catalytic pinacol coupling reactions, the role of chlorosilane is generally considered to cleavage the metal-oxygen bond of a putative pinacol formed to recycle the catalyst. However, they observed that TESCl provided better stereoselectivities than TMSCl in the catalyst system. This catalyst system represents the first example of the asymmetric catalysis of an aliphatic pinacol coupling reaction (Scheme 1.53).[69]



Scheme 1.53 Cr-catalyzed enantioselective pinacol coupling.

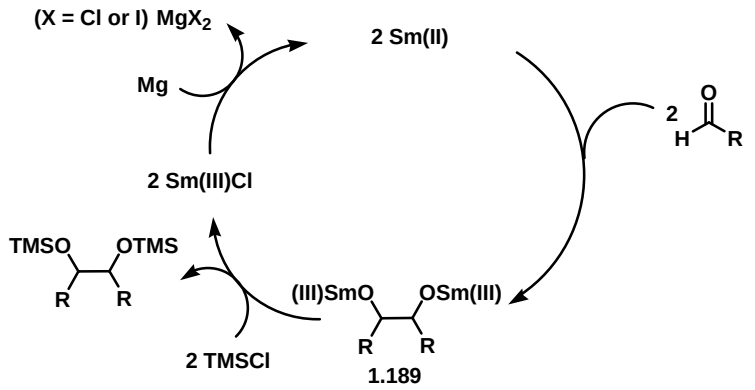
1.6.4 Samarium Catalysts

In 1996, the Endo group reported that Sm-catalyzed reductive coupling of aldehydes and ketones. In order to incorporate SmI_2 into the catalytic cyle, it is first required that samarium species must be reduced. Due to the similar reduction potential between Sm and Mg (-2.41 and -2.37 V, respectively), the possibility of Mg as reducing agent of trivalent samarium was investigated. Optimal conditions were found to be reaction of the aldehyde with a catalytic amount of SmI_2 in the presence of Mg/Me_3SiCl in THF. Aldehydes as well as ketones participated in the reaction to produce the corresponding products **1.186-1.188** in good yields. (Scheme 1.54).[70]



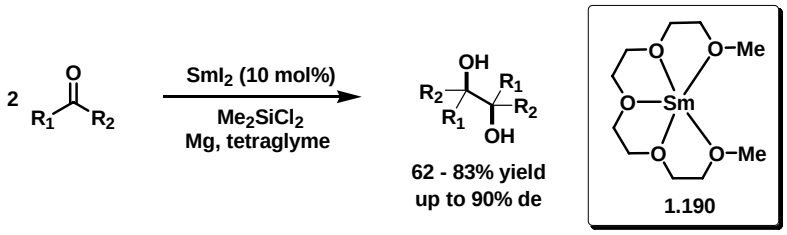
Scheme 1.54 Sm-catalyzed pinacol coupling.

On the basis that reactions employing both catalytic and stoichiometric SmI_2 exhibited the same level of diastereoselectivity, it was proposed that the carbon-carbon bond formation proceeds prior to silylation of the alkoxide. The possible reaction pathway involves the reduction of carbonyl compounds by SmI_2 to give Sm(III) alcoholates **1.189** followed by silylation of the alcoholates by TMSCl to provide the corresponding silyl ether and SmI_2Cl. SmI_2 or SmClI would be regenerated by the electron transfer from Mg (Scheme 1.55).



Scheme 1.55 Proposed catalytic cycle for Sm-catalyzed pinacol coupling.

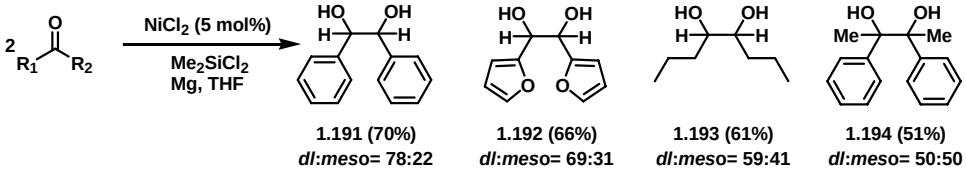
In 2005, the Greeves group reported the samarium-catalyzed diastereoselective pinacol coupling. To achieve high diastereoselectivity, a variety of potentially chelating ligands were screened. In the catalytic reaction, it is necessary for the chelating ligand to be sufficiently flexible to bind both the very large Sm^{2+} ion (eight-coordinate with radius of 141 pm) and the smaller Sm^{3+} ion (eight-coordinate with radius of 124 pm). It turned out that tetraglyme fulfilled this requirement to increase diastereoselectivity up to 90%. The author proposed the active catalyst for the pinacol coupling is Sm-tetraglyme complex **1.190** (Scheme 1.56).[71]



Scheme 1.56 Sm-catalyzed pinacol coupling using chelating ligand.

1.6.5 Other Catalysts (Nickel and Cesium)

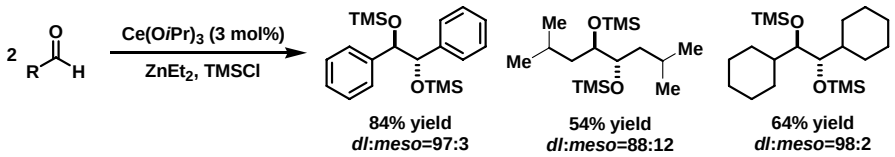
The Tu group found that Rieke Ni generated in situ was able to efficiently promote the pinacol coupling of various carbonyls. Additionally, the group examined the cheaper and more convenient $NiCl_2$(cat.)/Mg/TMSCl system for the pinacol coupling. Slow addition of a solution of the carbonyl compounds and TMSCl to the mixture of catalytic $NiCl_2$ and Mg afforded the pinacol coupling product **1.191** in 70% yield with a moderate diastreoselectivity. Heteroaryl aldehyde (**1.192**), alkyl aldehyde (**1.193**), and ketone (**1.194**) also participated in the reaction to produce dimerized products in good yields (Scheme 1.57).[72]



Scheme 1.57 Ni-catalyzed pinacol coupling.

In 2000, the Groth group demonstrated that cerium(III) isopropanolate catalyzed pinacol couplings of carbonyl compounds where diethylzinc is used as reducing agent. The advantages of this method are numerous. First, both aliphatic aldehydes and aromatic aldehydes can be coupled with high diastereoselectivities. Additionally, this method

allows pinacol preparation on a large scale which is of great interest for industrial applications. It is noteworthy that this reaction represents the first cerium-catalyzed reaction in organic chemistry (Scheme 1.58).[73]

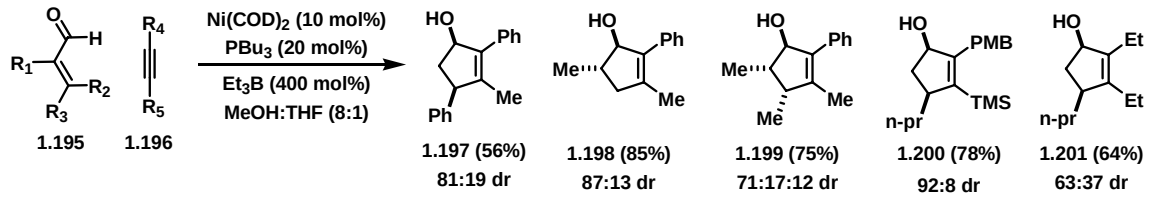


Scheme 1.58 Ce-catalyzed pinacol coupling.

1.7 MICELLANEOUS

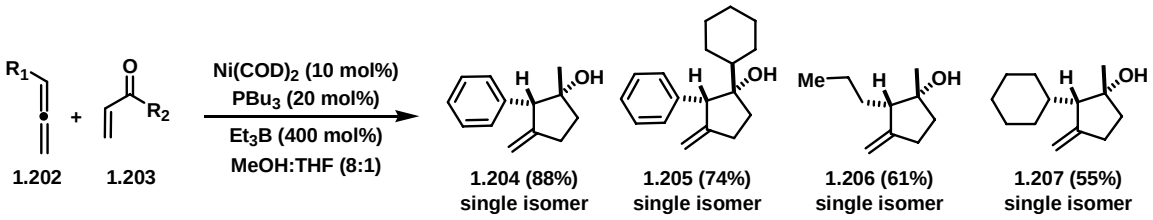
1.7.1 Reductive Cycloaddition

In 2000, Montgomery reported the stoichiometric nickel-promoted reductive [3+2] cycloaddition of tethered alkynes and enals.[74] The development of a catalytic variant of the reaction was found to be problematic due to competitive alkyne trimerization and difficulty in the reduction of Ni(II) to Ni(0) required to close the catalytic cycle. Upon screening various ligands and reaction conditions, it was found that a simple catalytic system involving triethylborane as a stoichiometric reductant, tributylphosphine as ligand, and a methanol/THF cosolvent system allowed the desired reductive [3+2] cycloaddition to proceed efficiently. The key for success requires that a Ni(0) species, a reducing agent (Et_3B), and a weak Brønsted acid (MeOH) can all coexist under the reaction conditions. A wide range of conjugated enals **1.195** underwent catalytic diastereo-selective and regioselective [3+2] cycloaddition with internal alkynes **1.196** to produce the reductive cycloaddition products **1.197-1.201** in good yields and good diastereo-selectivies (Scheme 1.59).[75]



Scheme 1.59 Ni-catalyzed reductive cycloaddition of alkynes and enals.

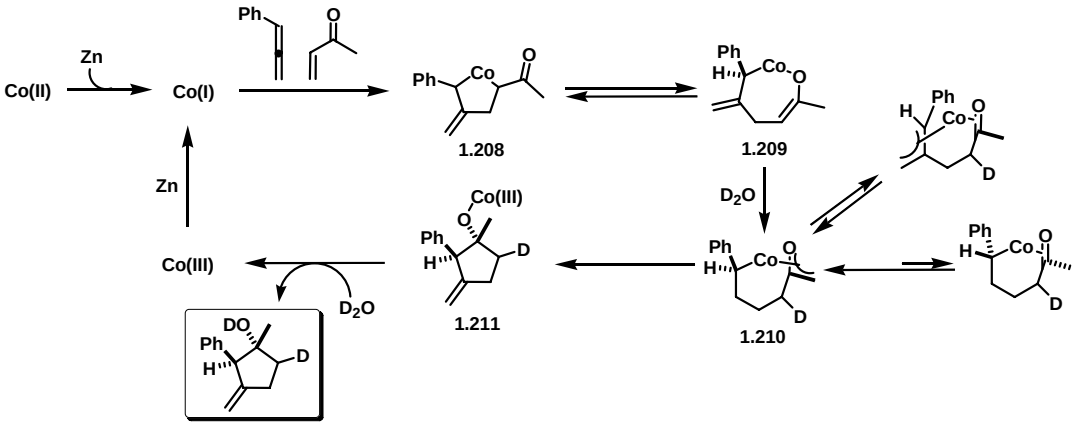
More recently, Cheng reported a cobalt-catalyzed diastereoselective reductive [3+2] cycloaddition of allenes and enones. Treatment of allenes **1.202** with α,β-unsaturated ketones **1.203** in the presence of CoI_2(dppe), Zn, ZnI_2, and water in CH_3CN gave cyclopentanol derivatives **1.204-1.207** in very good yields with excellent chemo- and regioselectivity. In all cases, the cycloaddition took place exclusively at the terminal double bond placed at the 3-position of cyclopentanol. (Scheme 1.60).[76]



Scheme 1.60 Co-catalyzed reductive cycloaddition of allenes and enones.

To understand the role of water and to elucidate the mechanism of the reaction, an isotope labeling using D_2O was carried out. The results showed that the 5-position on the cyclopentanol ring and the alcohol were both deuterated. Based on the deuterium labeling results, a plausible mechanism was proposed. The catalytic cycle is initiated by the reduction of Co(II) to Co(I) by zinc dust. Next, the chemoselective cyclometallation of Co(I) with allene and enone forms cobaltacyclopentane intermediate **1.208**. Selective protonation of **1.209** followed by carbonyl insertion into the cobalt-carbon bond produces

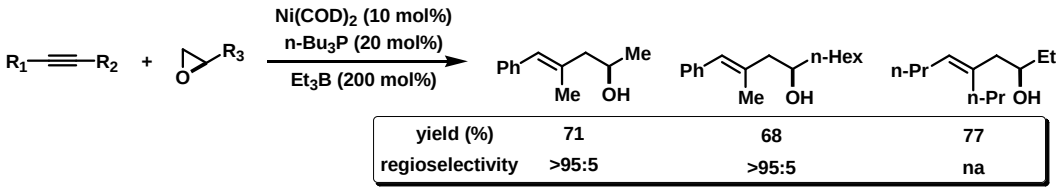
the cobaltalkoxide **1.210**. Subsequent protonation of alkoxide **1.211** leads to the observed product (Scheme 1.61).



Scheme 1.61 Proposed catalytic cycle for Co-catalyzed reductive cycloaddition.

1.7.2 Reductive Coupling of Alkynes and Epoxides

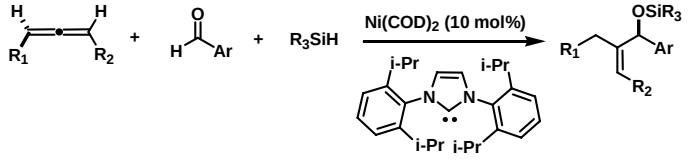
In 2003, Jamison reported a Ni-catalyzed reductive coupling of alkynes and epoxides. Exposure of alkyne and chiral epoxide to nickel(0) in the presence of Et_3B provided homoallylic alcohols in moderate yields with high regioselectivity. While there was little dependence of yield upon solvent choice, maximum yield was obtained in the absence of traditional organic solvent. In addition, it was noteworthy that the optical purity is fully preserved in this reductive coupling (Scheme 1.62).[77]



Scheme 1.62 Ni-catalyzed reductive coupling of alkynes and epoxides.

1.7.3 Reductive Coupling of Allenes and Aldehydes

In 2005, Jamison reported a highly enantioselective and regioselective Ni-catalyzed reductive coupling of allenes and aldehydes. In examining combinations of allenes, aldehydes, and reducing agents, a $Ni(COD)_2$-Cyp_3P-Et_3SiH system turned out to be excellent for chemoselectivity (the ratio of allylic and homoallylic products was >95:5), but the enantioselectivity was seriously decreased from 95 to 62% ee. However, it was found that the use of $Ni(COD)_2$-imidazolinyl carbene-R_3SiH system completely eliminated this limitation to give the coupling product in good yields and excellent enantioselectivies. Additionally, they documented full transfer of allene axial chirality in the reductive coupling reaction. The reactivity and substrate scope are summarized in Scheme 1.63.[78]

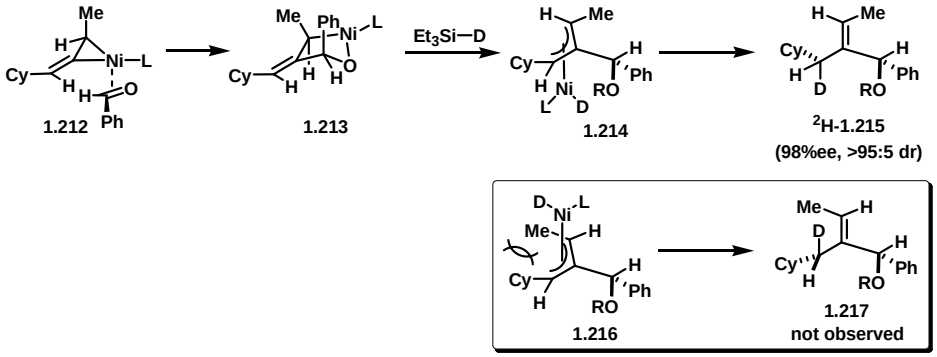


	OSiEt$_3$ n-Pr n-Pr	OSiR$_3$ n-Pr n-Pr Cl	OSiR$_3$ c-Hex Me	OSiR$_3$ t-Bu Me
yield (%)	80	66	76	40
regioselectivity (allylic:homoallylic)	94:6	90:10	97:3	85:15
site selectivity	na	na	>95:5	>95:5
ee (%)	95	95	98	98

Scheme 1.63 Ni-catalyzed reductive coupling of allenes, aldehydes, and silanes.

Mechanistically, it is believed that there is a direct link between the selectivity for the (*Z*)-alkene geometry and the sense of induction of deuterium labeling. σ-Bond metathesis between **1.213** and Et_3SiD could afford η^3-allyl-Ni complex **1.214**. Reductive

elimination with retention leads to the observed (*Z*)-alkene and (*R*)-configuration at the labeled carbon (**1.215**). On the other hand, the alternative complex **1.216** gives the opposite sense of selectivity in both cases ((*E*)and (*S*), respectively). The absence of (*E*,*S*)-product **1.217** can be explained by the severe 1,3-interaction between the Me and Cy groups present in complex **1.216** (Scheme 1.64).

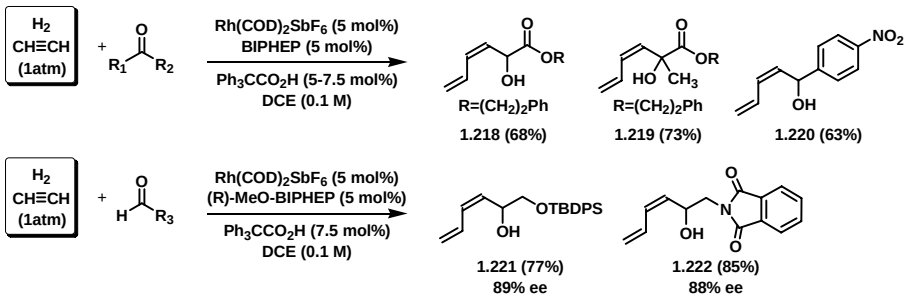


Scheme 1.64 Plausible reaction pathways supported by ^{2}H-labeling.

1.7.4 Multicomponent Reductive Coupling of Acetylene and Carbonyls

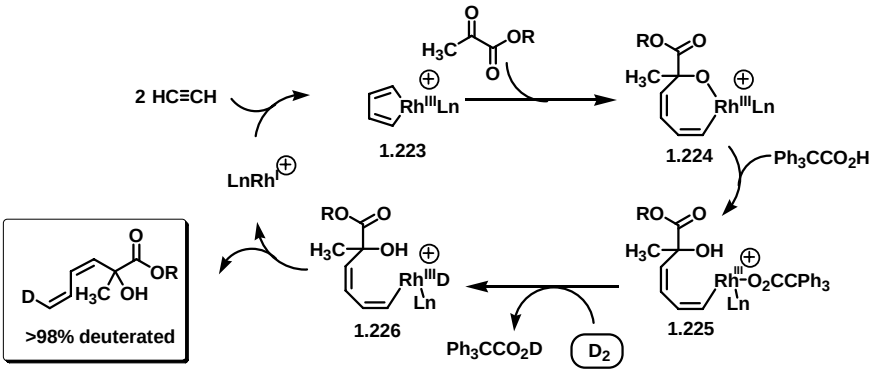
More recently, the Krische group demonstrated the multicomponent reductive coupling of acetylene with carbonyl compounds. Exposure of phenethyl glyoxalate to equal volumes of hydrogen and acetylene gas in the presence of $Rh(COD)_2OTf$ (5 mol%), triphenylacetic acid (TPAA, 5 mol%) as cocatalyst, and BIPHEP as a ligand produced carbonyl (*Z*)-butadienylation product **1.218** in 32% yield. It was found that the cationic rhodium(I) counterion played a decisive role. As expected, precatalysts possessing chloride counterions provided none of the reductive coupling product. However, in the series $Rh(COD)_2X$, where the counterion X is OTf, BF_4, SbF_6, and BARF ($B(3,5\text{-}(CF_3)_2C_6H_3)_4$, counterions that coordinate to the rhodium metal less strongly than OTf uniformly provided the coupling product **1.218** in higher yield. These

optimized conditions were applied successfully to a diverse set of carbonyl partners. α-Ketoester and aromatic aldehydes successfully participated in the reductive coupling to produce the corresponding products **1.219** and **1.220** in good yields. Moreover, enantioselective (*Z*)-butadienylation of aldehydes using (*R*)-MeO-BIPHEP as a chiral ligand produced the corresponding coupling products **1.221** and **1.222** in 88% ee and 89% ee, respectively (Scheme 1.65).[79]



Scheme 1.65 Reductive coupling of acetylene and carbonyls.

As corroborated by deuterium labeling studies, the catalytic mechanism likely involves oxidative dimerization of two acetylene molecules to form a rhodacyclopentadiene **1.223** followed by carbonyl insertion. Subsequent protonolytic cleavage of the oxarhodacycloheptadiene **1.224** by the acid co-catalyst gives rise to a vinyl rhodium carboxylate **1.225**, which upon hydrogenolysis through a six-centered transition structure and C-D reductive elimination of rhodium deuteride **1.226** delivers the coupling product (Scheme 1.66). In order to further confirm the mechanistic probe, ESI-MS studies were conducted. As shown in Figure 4.2, the most abundant ions, as assigned on the basis of their m/z values, correspond to species postulated to arise in the proposed catalytic cycle shown in Scheme 1.66. These results strongly support the proposed catalytic mechanism.



Scheme 1.66 Plausible catalytic mechanism as supported by ^{2}H-labeling.

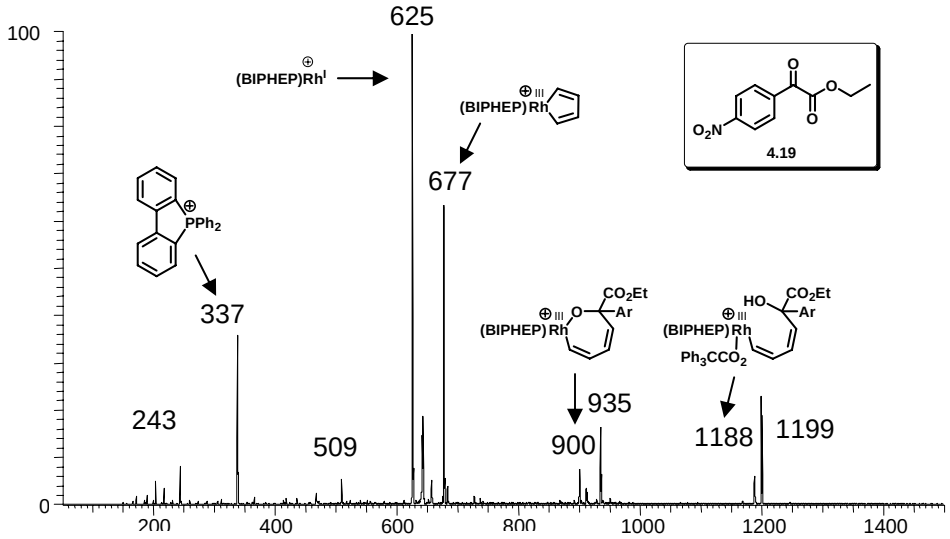


Figure 1.3 ESI Mass full scan spectrum.

1.8 SUMMARY AND OUTLOOK

Over the past decade, catalytic intermolecular reductive couplings have evolved into a broadly useful strategy for assembling synthetically versatile substructures and complex molecules. In this regard, the reductive coupling technology has added valuable processes to the synthetic toolbox. Yet, we have barely scratched the surface of immense possibilities afforded by catalytic intermolecular reductive coupling technology. Future challenges will be the development of cross coupling of alkenes, cross coupling of alkynes, and coupling of simple alkenes (not conjugated alkene) with aldehydes. Finally, the further evolution of catalytic intermolecular reductive couplings will provide a robust technology to obtain useful organic compounds from easily accessible starting materials, while using more "green" chemistry and addressing issues of atom economy, cost effectiveness, and environmentally safe methods.

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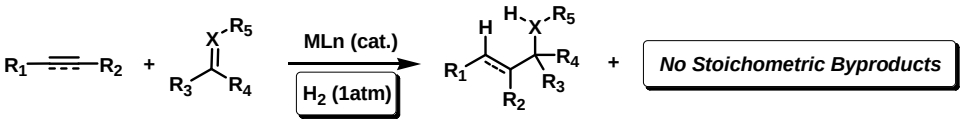
Chapter 2 Hydrogen-Mediated Carbon-Carbon Bond Formation: Discovery and Development

2.1 INTRODUCTION

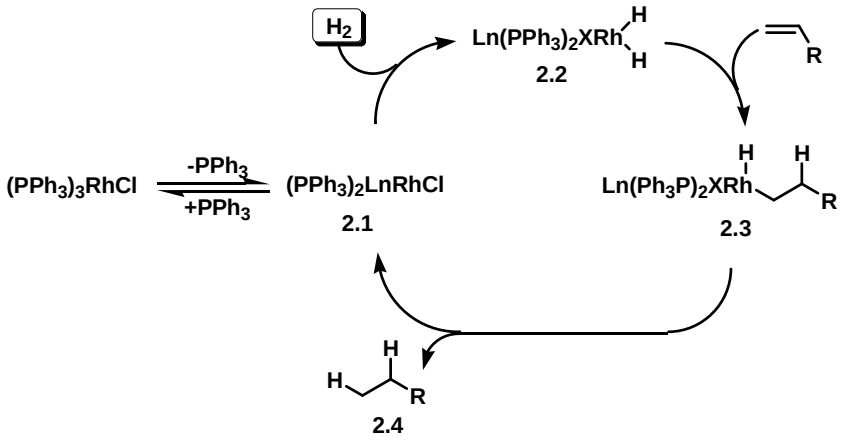
At the threshold of the 21st centry, a new set of challenges was defined by the need to develop a sustainable means of preparing the chemical commodities demanded by our society. Hence, such concepts as atom economy,[1] step economy, and "green chemistry"[2] have become essential requirements for the development of any synthetic reaction. Additionally, the utilization of a set of principles that avoids the use of stoichiometric reagents and creation of wasteful chemical byproducts is of importance. Hydrogenation is one of the most powerful catalytic methods that can statisfy these requirements.[3] Accordingly, catalytic hydrogenation has been tremendously utilized industrially, accounting for over half of the chiral compounds made by man not produced *via* physical or enzymatic resolution.[4] The profound impact of hydrogenation portended a powerful approach to reductive carbon-carbon bond formation under hydrogenation conditions and resulted in the discovery of the Fischer-Troph process[5] and hydroformylation.[6] However, these processes are restricted to the incorporation of carbon monoxide. Therefore, the field of the reductive C-C bond formation under hydrogenation conditions has lain fallow for several decades. Even though there have been a few seminal contributions,[7] systematic efforts toward the development of hydrogen-mediated carbon-carbon bond formation process beyond hydroformylation have been absent from the literature. Given the profound potential impact of the hydrogen-mediated C-C bond formation, the Krische group has initiated systematic efforts towards the development of hydrogen-mediated C-C bond formation (Scheme 2.1).



Scheme 2.1 Hydrogen-mediated C-C bond formation.

2.2 HYDROGENATIVE C-C BOND FORMATION BEYOND HYDROFORMYLATION

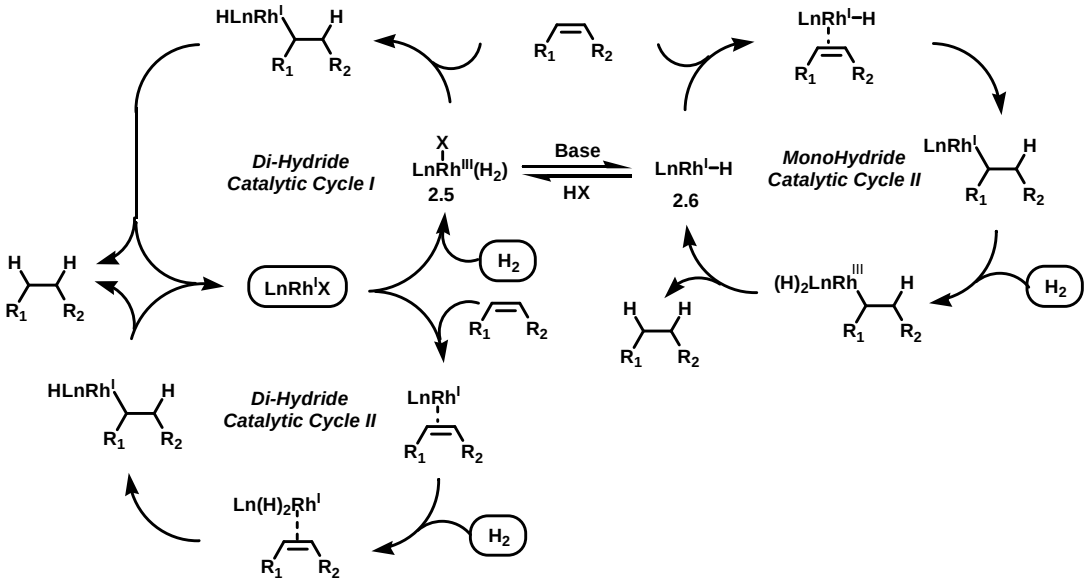
To investigate the feasibility of hydrogen-mediated C-C bond formations, it is necessary to review conventional hydrogenation.[3] Among catalysts for conventional hydrogenation, rhodium catalysts have been studied in greatest detail. For conventional hydrogenation, there are three fundamental steps: (1) oxidative addition of hydrogen to metal complex (2) hydrometallation of substrate (3) C-H reductive elimination. The mechanism of alkene hydrogenation catalyzed by the neutral rhodium complex $RhCl(PPh_3)_3$ (Wilkinson's catalyst) has been studied in detail by Halpern.[8] In the catalytic cycle, the oxidative addition of hydrogen to rhodium complex **2.1** generates a dihydrido rhodium complex **2.2**. Then hydrometallation of the alkene produces organomonohydrido rhodium complex **2.3**. It is believed that the hydrogen oxidative addition step is a reversible process and the turnover-limiting step. Finally, rapid C-H reductive elimination produces the hydrogenation product **2.4** and regenerates the catalyst **2.1**. To achieve carbon-carbon bond formation under hydrogenation conditions, it is necessary to intercept the hydrometallated intermediate **2.3** arising transiently in the course of catalytic hydrogenation. However, the possibility of C-C coupling is very low due to the rapid C-H reductive elimination (Scheme 2.2).



Scheme 2.2: Hydrogenation catalyzed by Wilkinson's catalyst.

Cationic rhodium complexes however, exhibit different characteristics under hydrogenation conditions. The hydrogenation of simple alkenes using cationic rhodium precatalysts has been studied in detail by Osborn and Schrock.[9] Although there is no kinetic data, their collective experimental data suggest that both monohydride-based and dihydride-based catalytic cycles are operative. It was also documented that monohydride-based and dihydride-based catalytic cycles may be partitioned by virtue of an acid-base reaction involving deprotonation of cationic rhodium(III) dihydride **2.5** to furnish a neutral rhodium (I) monohydride species **2.6** (Scheme 2.3). In addition, it was also observed that alkene isomerization occurred under hydrogenation conditions using a cationic rhodium complex.[9(a)] From Osborn and Schrock's studies, the Krische group extracted two important facts concerning cationic rhodium complexes. First of all, rhodium monohydride-based catalytic cycle may operate in presence of base additives. Secondly, substrate hydrometallation from the rhodium monohydride complex **2.7** furnishes organometallic intermediate **2.8** which lacks hydride ligands. This should disable direct C-H reductive elimination manifolds, and extend the lifetime of the resulting organometallic intermediate **2.8** to facilitate its capture by electrophilic partners.

These two pieces of information strongly support the possibility of C-C bond formation under hydrogenation conditions using cationic rhodium complexes in the presence of base additives (Scheme 2.4(a)).

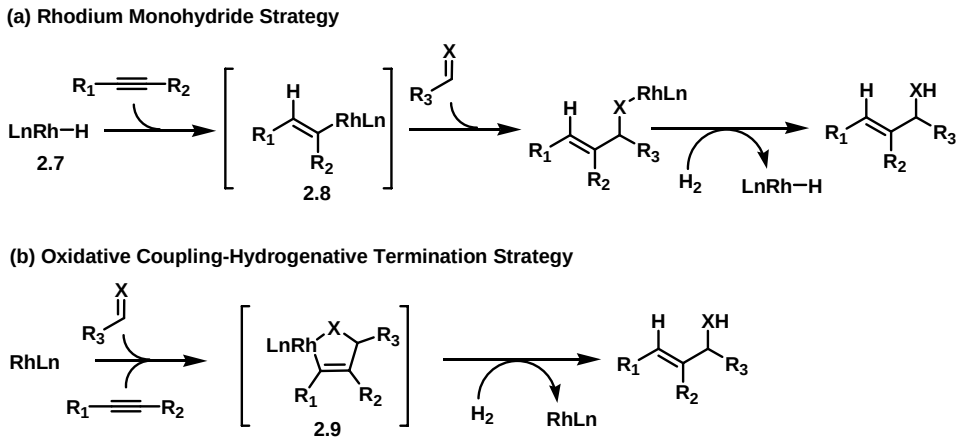


Scheme 2.3: Hydrogenation catalyzed by a cationic rhodium complex.

An alternative pathway involves oxidative coupling of two or more organic molecules to furnish a metallocycle **2.9**, an intermediate which is well known in other rhodium catalyzed coupling reactions.[10] In this pathway, C-C bond formation precedes hydrogen activation to form the metallocycle **2.9**. Subsequently, σ-bond metathesis[11] with hydrogen provides the reductive coupling product and regenerates the catalyst. This hypothesis is further supported by the fact that cationic rhodium complexes are slow to activate hydrogen, so oxidative coupling of the reactants may precede hydrogen activation leading to carbon-carbon bond formation products (Scheme 2.4(b)).

On the basis of the mechanistic analysis of rhodium catalyzed conventional hydrogenation and the general properties of cationic rhodium complexes, the Krische

group identified two possible pathways for hydrogen-mediated C-C bond formation: (1) the rhodium monohydride strategy and (2) the oxidative coupling-hydrogenative termination strategy (Scheme 2.4).



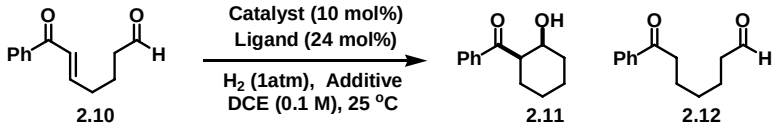
Scheme 2.4 Potential pathways for hydrogen-mediated C-C bond formation.

2.3 RHODIUM MONOHYDRIDE STRATEGY

2.3.1 Intramolecular Reductive Aldol Cyclization

To investigate the idea of the rhodium monohydride strategy, the Krische group examined an intramolecular reductive aldol reaction under hydrogenation conditions. As expected, hydrogenation of the phenyl-substituted mono-enone mono-aldehyde **2.10** using neutral rhodium (I) catalyst $Rh(PPh_3)_3Cl$ furnished the conventional enone hydrogenation product **2.12**. However, cationic rhodium(I) complexes with the electron deficient phosphine $(p\text{-}CF_3Ph)_3P$, and the base additive KOAc smoothly catalyzed the reductive aldol cyclization to produce *syn*-aldol product **2.11** in 89% yield and good diastereoselectivity. The pronounced effect of basic additives on partitioning of the aldolization and 1,4-reduction manifolds suggests that the enolate-hydrogen reductive

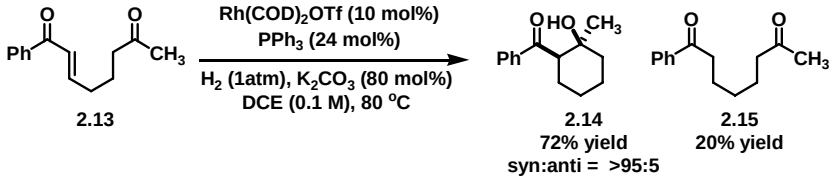
elimination pathway are suppressed through deprotonation of the (hydrido)metal intermediates $LnRh^{III}X(H)_2$ or (enolate)$Rh^{III}X(H)Ln$. Thus, as observed by Osborn and Schrock, deprotonation mediated by base additives changes the catalytic mechanism from a dihydride-based cycle to a monohydride-based cycle (Scheme 2.5).[9]



Entry	Catalyst	Ligand	Additive (mol%)	Yield (syn:anti)	1,4-reduction
1	$Rh(PPh_3)_3Cl$	None	None	1 (99:1)	57
2	$Rh(COD)_2OTf$	PPh_3	None	21 (99:1)	25
3	$Rh(COD)_2OTf$	PPh_3	KOAc (30)	59 (58:1)	21
4	$Rh(COD)_2OTf$	$(pCF_3Ph)_3P$	None	57 (14:1)	22
5	$Rh(COD)_2OTf$	$(pCF_3Ph)_3P$	KOAc (30)	89 (10:1)	0.1

Scheme 2.5 Reductive aldol cyclization of mono-enone mono-aldehyde.

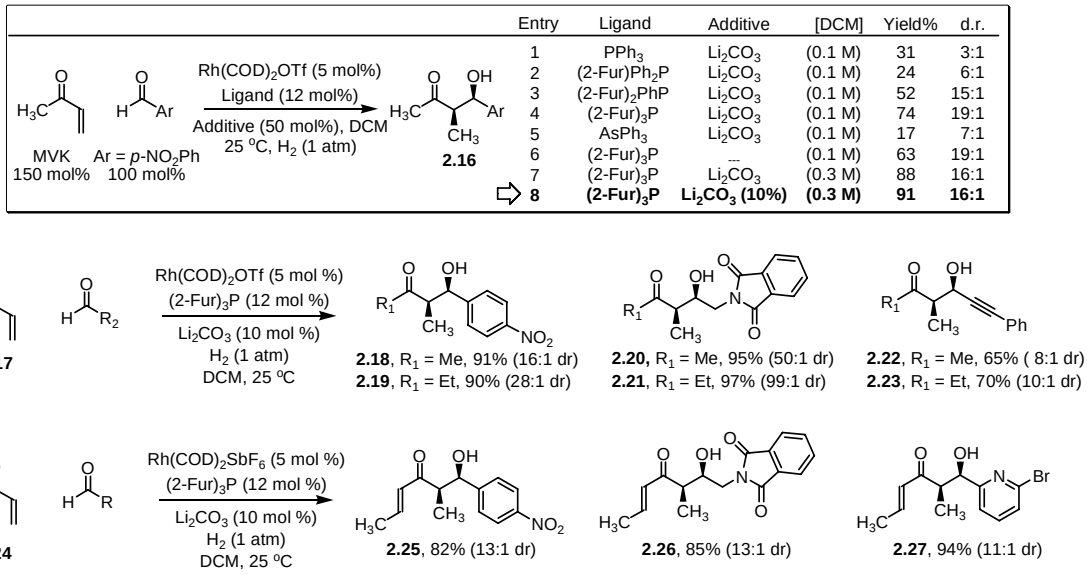
This intramolecular reductive aldol reaction[12] was further extended to the reductive cyclization of monoenone monoketone substrates. The Rh-catalyzed reductive aldol cyclization of monoenone monoketone **2.13** provided the desired product **2.14** in 72% yield and with excellent diastereoselectivity. In general, for the reductive aldol cyclization of keto-enones, the competitive 1,4-reduction product **2.15** was observered in response to the reduced reactivity of the electrophilic partner (Scheme 2.6).[13]



Scheme 2.6 Reductive aldol cyclization of mono-enone mono-ketone.

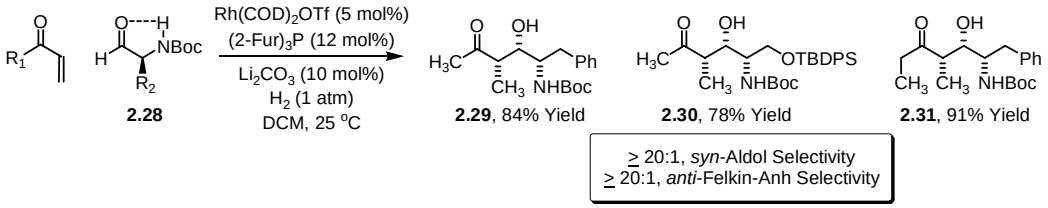
2.3.2 Intermolecular Reductive Aldol Coupling

Intermolecular reductive aldol coupling using triphenylphosphine (Ph_3P) ligated cationic rhodium catalysts provided aldol products in good yields, but with poor levels of diastereoselectivity.[12] Upon screening of monodentate phosphine ligands, it was found that tri-2-furylphosphine ligated cationic rhodium catalysts gave the reductive aldol coupling products **2.16** in good yield and with high levels of *syn*-diastereoselectivity. Additionally, it was observed that the basic additive Li_2CO_3 played a critical role for high *syn*-diastereoselectivity. Under the optimized conditions, commercially available methyl and ethyl vinyl ketone **2.17** and divinyl ketones such as crotyl vinyl ketone **2.24** engaged in highly diastereoselective reductive aldol coupling with a diverse collection of aldehydes to produce the reductive aldol coupling products **2.18**-**2.23** and **2.25**-**2.27** in good to excellent yields and with excellent diastereoslectivities (Scheme 2.7).[14]



Scheme 2.7 Hydrogen-mediated intermolecular reductive aldol coupling.

Inspired by the high stereoselectivity of reductive aldol couplings, the Krische group studied the generation of stereotriads by way of reductive aldol couplings to optically enriched α-chiral aldehydes. Hence, the hydrogenation of vinyl ketones in the presence of *N*-Boc-α-aminoaldehydes **2.28** at ambient temperature resulted in the formation of aldol stereotriads **2.29**-**2.31** that embody high levels of *syn*-aldol diastereoselectivity accompanied by high levels of *anti*-Felkin-Ahn control. Presumably, intramolecular hydrogen bonding of *N*-Boc-α-aminoaldehydes might be responsible for the high levels of *anti*-Felkin-Ahn control (Scheme 2.8).[15]

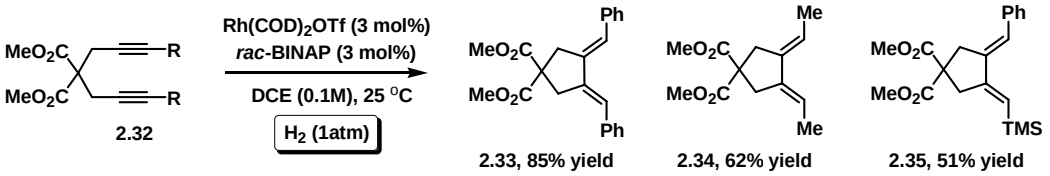


Scheme 2.8 Hydrogen-mediated reductive aldol coupling to α-aminoaldehydes.

2.4 OXIDATIVE COUPLING-HYDROGENATIVE TERMINATION STRATEGY

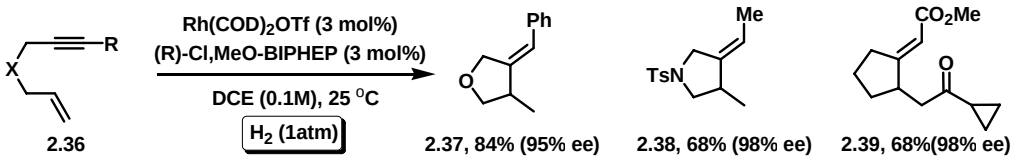
2.4.1 Reductive Cyclization

To investigate the idea of the oxidative coupling-hydrogenative termination strategy, the Krische group examined the reductive cyclization of 1,6-diynes under hydrogenation conditions. Catalytic hydrogenation of 1,6-diynes **2.32** employing cationic rhodium precatalysts at ambient hydrogen pressure enabled the reductive carbocyclization to produce 1,2-dialkylidene cyclopentanes **2.33**-**2.35** in good to excellent yields as single alkene stereoisomers (Scheme 2.9).[16]



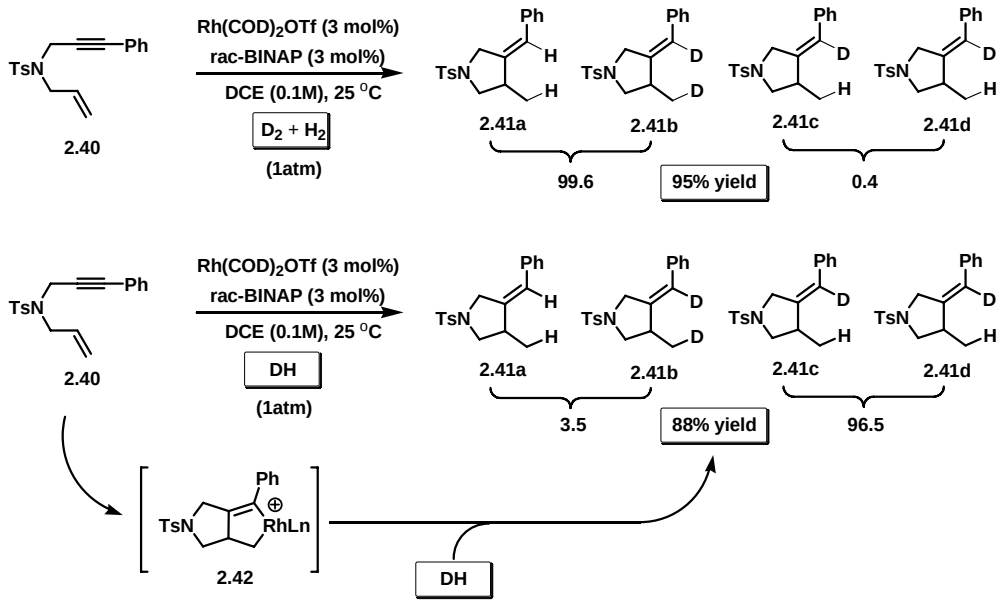
Scheme 2.9 Reductive cyclization of 1,6-diynes.

This method has successfully extended to the reductive cyclization of 1,6-enynes. Moreover, the entantioselective reductive cyclization of 1,6-enynes was investigated by employing chiral phosphine ligands. Among the chiral triarylphosphines assayed, the reductive cyclization of 1,6-enyne **2.36** using (*R*)-Cl-MeO-BIPHEP provided the desired products **2.37-2.39** in good yields and excellent enantioselectivities (Scheme 2.10).[17]



Scheme 2.10 Enantioselective reductive cyclization of 1,6-enynes.

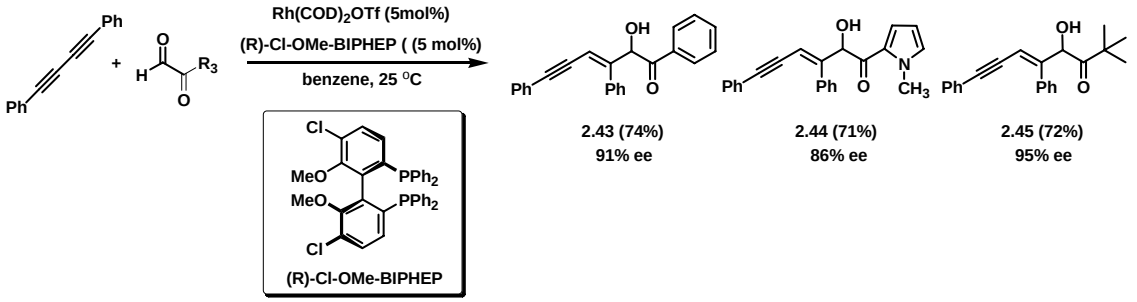
To gain mechanistic insight, deuterium labeling studies and H/D crossover experiments were conducted. Based on deuterium labeling studies, the formal heterolytic activation mechanism (rhodium monohydride mechanism) could be ruled out. It is assumed that oxidative coupling of a cationic rhodium complex with 1,6-enyne **2.40** preceed hydrogen activation to afford a metallocycle intermediate **2.42**, and subsequent hydrogenaction *via* σ-bond metathesis followed by C-H reductive elimination produces the desired products **2.41a**-**2.41d** (Scheme 2.11). Indeed, the rhodacyclopentadiene intermediate and the rhodacyclopentene intermediate such as **2.42** are well known in literature.[10,18]



Scheme 2.11 Crossover experiments in the absence of base.

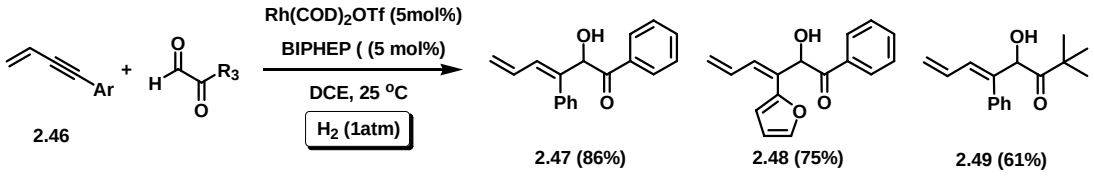
2.4.2 Intermolecular Reductive Coupling

To investigate the possibility of an oxidative coupling-hydrogenative termination strategy in the intermolecular system, the reductive coupling of diynes and activated aldehydes was examined as a model system. Treatment of diphenylbutadiyne with phenyl glyoxal in the presence of catalytic $[Rh(COD)_2]OTf$ in dichloroethane afforded the conjugated diene product in good yield as a single regio- and stereoisomer. To explore the feasibility of an enantioselective variant, a variety of commercially available chiral triarylphosphine ligands were screened. Among the chiral triarylphosphines assayed, (*R*)-Cl-MeO-BIPHEP proved superior, providing the coupling product **2.43** in 74% yield and 76% ee. Through variation of the reaction medium, benzene was identified as the ideal solvent, affording a 74% yield of **2.43** in 91%ee. Heteroaryl glyoxal and alkyl glyoxal also participated in the reaction to produce the corresponding products **2.44** and **2.45** in 86% ee and 95%ee, respectively (Scheme 2.12).[19]



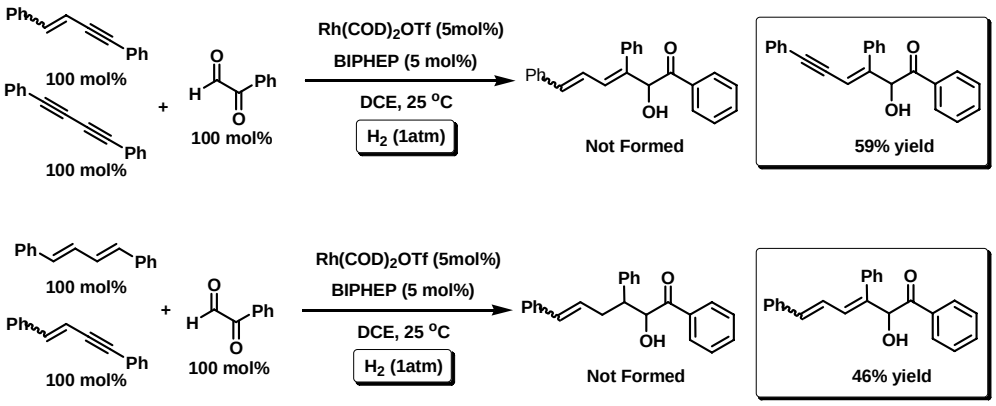
Scheme 2.12 Asymmetric reductive coupling of 1,3-diynes and glyoxals.

The reductive coupling of 1,3-diynes and activated aldehydes was further extended to the reductive coupling of 1,3-enynes and α-ketoaldehydes. Exposure of 1,3-enyne **2.46** to phenyl glyoxal under an atmosphere of hydrogen in the presence of $Rh(COD)_2OTf$ and BIPHEP in DCE provided the highly unsaturated diene-containing product **2.47** in 86% yield as a single regio- and stereoisomer. In addition, the reductive coupling to heteroaryl and alkyl glyoxal provided the corresponding products **2.48** and **2.49** in good yields (Scheme 2.13).[20]



Scheme 2.13 Reductive coupling of 1,3-enynes and glyoxals.

To gain insight into the origin of the chemo- and regioselectivity observed for the intermolecular reductive coupling of conjugated alkynes with α-ketoaldehydes, a series of competition experiments were performed. It was found that the diyne is the most reactive, and the enyne is more reactive than the diene (Scheme 2.14). Chemo-selective coupling to the more highly unsaturated pronucleophile suggests preferential coordination of the most π-acidic reacting partner by low-valent rhodium, as explained by the Dewar-Chatt-Duncanson model for alkyne coordination.[21]



Scheme 2.14 Competition experiments.

2.5 SUMMARY AND CONCLUDING REMARKS

The results of reductive aldol reaction *via* rhodium monohydride strategy and results of reductive coupling of conjugated alkynes with a set of activated aldehydes *via* oxidative coupling-hydrogenative termination strategy proved the feasibility of carbon-carbon bond formation under hydrogenation conditions. This novel reductive coupling methodology involves the electrophilic trapping of organometallic intermediates during the course of catalytic hydrogenation, forming π-unsaturated products without over-reduction. The following chapter will describe the extension of the scope of this new reaction.

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Chapter 3 Rh-Catalyzed Reductive Coupling of Conjugated Alkynes with Iminoacetates and α-Ketoesters

3.1 INTRODUCTION

The results of hydrogen mediated reductive coupling of conjugated alkynes with a set of activated aldehydes prove the feasibility of the oxidative coupling-hydrogenative termination strategy.[1] This novel reductive coupling methodology involves the electrophilic trapping of organometallic intermediates during the course of catalytic hydrogenation, forming π-unsaturated products without over-reduction. The use of elemental hydrogen in this class of reactions has potentially overcome the disadvantages of many hydrometallative reductive coupling methods which generate stoichiometric byproducts.[2] These preliminary findings stimulated efforts toward related transformations involving imines and ketones as electrophilic partners. In this section, we report three different types of hydrogen-mediated reductive couplings: (1) intermolecular reductive coupling of 1,3-enynes with iminoacetates, (2) intermolecular reductive coupling of 1,3-diynes with iminoacetates, (3) intermolecular reductive coupling of 1,3-enynes with α-ketoesters.

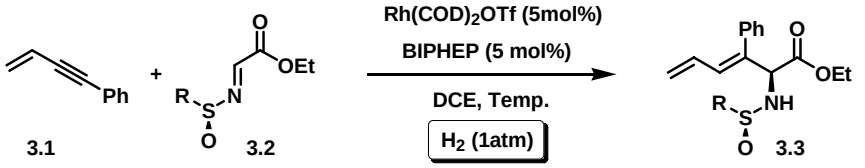
3.2 REDUCTIVE COUPLING OF 1,3-ENYNES WITH IMINOACETATES

3.2.1 Optimization

To investigate the possibility of Rh-catalyzed reductive coupling of 1,3-enynes to imines under hydrogenation conditions, our initial efforts focused on the hydrogen-mediated reductive coupling of 1,3-enyne **3.1** (200 mol%) to assorted (*N*-sulfinyl)-iminoacetates **3.2** (100 mol%) at ambient pressure and temperature in the presence of $Rh(COD)_2OTf$ (5 mol%) and BIPHEP (5 mol%) in dichloromethane (0.1M). It was found

that hydrogenation of **3.1** in the presence of ethyl (*N-para*-toluenesulfinyl)iminoacetate **3.2a**[3] (100 mol%) provided the desired reductive coupling product **3.3a** in 95% yield, but with poor diastereoselectivity. A further decrease in diastereoselectivity is observed in conjunction with the use of the corresponding mesityl derivative **3.2b**. However, hydrogenation of 1,3-enyne in the presence of ethyl (*N-tert*-butanesulfinyl)iminoacetate **3.2c**[4] furnished the desired reductive coupling product **3.3c** in 55% yield as a single regio- and stereoisomer. When the reaction was conducted at higher concentration (0.3M), the yield was increased to 92% without loss of selectivity. Finally, at a slightly elevated temperature (35 ^{o}C), the desired product was obtained in 99% yield as a single diastereomer (Table 3.1).

Table 3.1 Optimization table of reductive coupling of 1,3-enynes and iminoacetates.



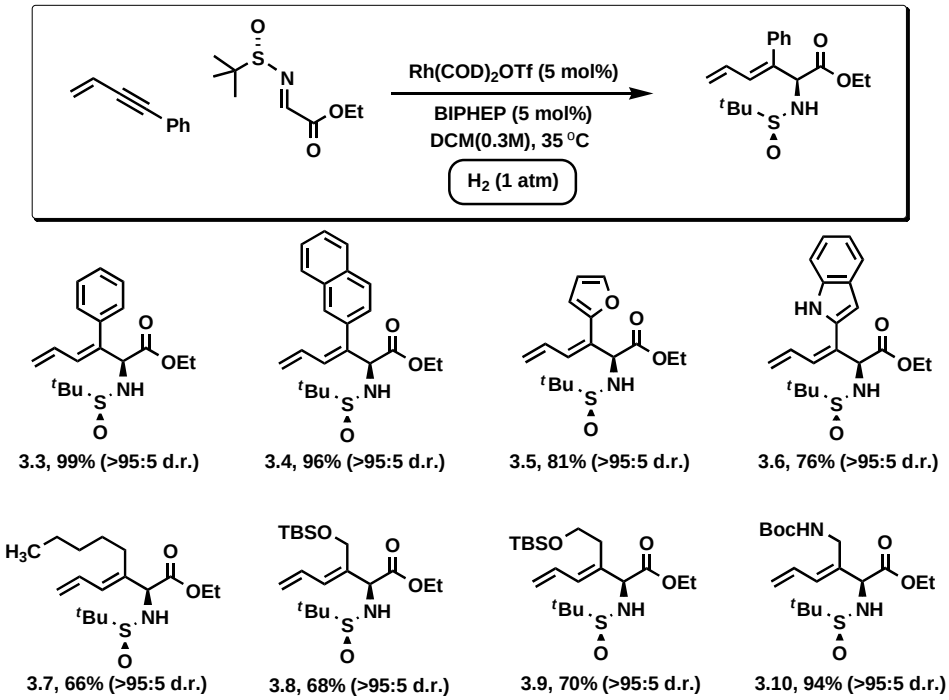
entry	R	concentration	temp (^{o}C)	yield (%)	dr
1	Tolyl (3.2a)	0.1	24	95 (3.3a)	3.4:1
2	Mesityl (3.2b)	0.1	24	96 (3.3b)	1.2:1
3	tert-Butyl (3.2c)	0.1	24	55 (3.3c)	>95:5
4	tert-Butyl (3.2c)	0.3	24	92 (3.3c)	>95:5
5	tert-Butyl (3.2c)	0.3	35	99 (3.3c)	>95:5

3.2.2 Substrate Scope

Using optimized conditions in Table 3.1, various conjugated alkynes were tested with ethyl (*N-tert*-butanesulfinyl)iminoacetate **3.2c**. As indicated in Table 3.2, aryl

enynes and heteroaryl enynes worked very well to produce the corresponding products **3.3**-**3.6** in good to excellent yields and with >95:5 regio- and diastereoselecitvity. In addition, alkyl enynes smoothly underwent the reductive coupling to produce the desired products **3.7**-**3.10** in good yields with high diastereoselectivities. The chemoselectivity of the hydrogen-mediated coupling of enynes to iminoacetates underscored by the fact that over-reduction of the diene-containing products was not observed.

Table 3.2 Reductive coupling of 1,3-enynes and iminoacetates.[5]



The regio- and stereochemical assignment of reductive coupling products was confirmed by a single crystal X-ray analysis of a derivative of compound **3.6** prepared from the exhaustive hydrogenation of the coupling product **3.6** using Crabtree's catalyst $[Ir(COD)(Pyr)(PCy)_3]PF_3$ at ambient pressure and temperature (Figure 3.1).

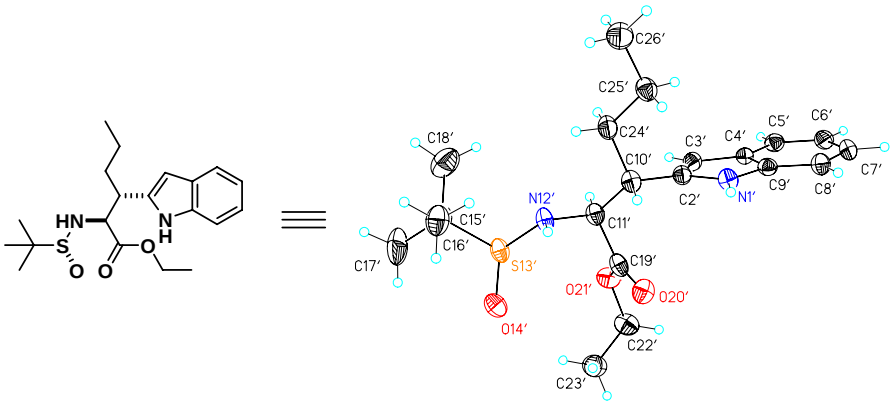


Figure 3.1 X-ray structure of a derivative of compound **3.6**.

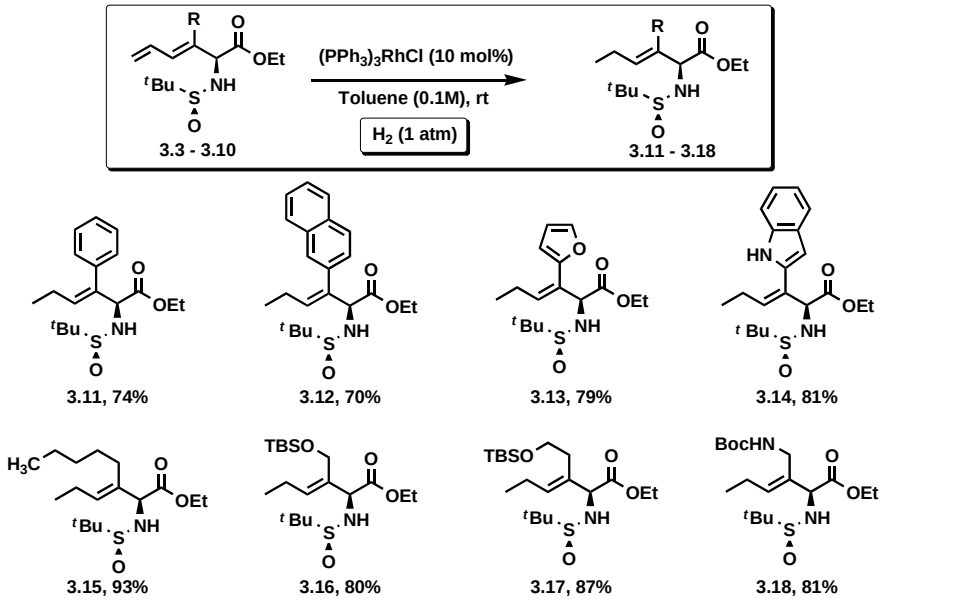
3.2.3 Elaboration of Reductive Coupling Products

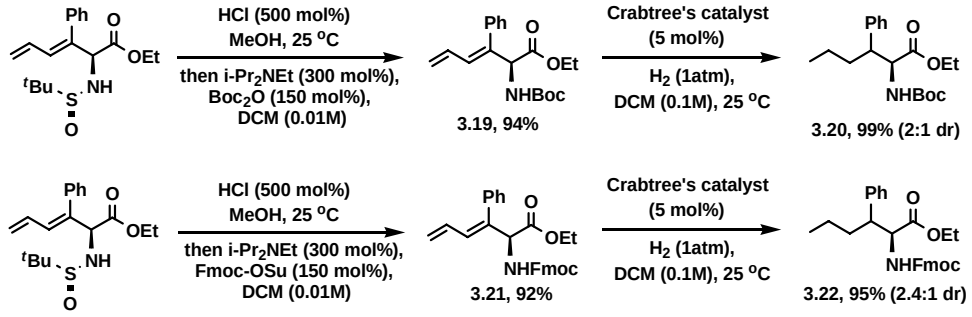
In a preliminary effort to explore further manipulation of the coupling products, compound **3.3** was exposed to $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) at ambient pressure and temperature. In the event, regioselective hydrogenation of the coupling product **3.3** occurred cleanly to afford the β,γ-unsaturated α-amino esters **3.11** in 74% yield. These regioselective hydrogenation conditions were applied to all diene-containing products. Under optimized conditions, the β,γ-unsaturated α-amino esters **3.12-3.18** were obtained in 70-93% yields (Table 3.3).

Conversion of the coupling product **3.3** to the corresponding Boc-derivative was explored next. The conversion worked excellently to produce the compound **3.19** in 94% yield. Similarly, conversion to Fmoc was conducted to give the compound **3.21** in 92% yield. Next, exhaustive hydrogenation of the diene side chain was explored. Hydrogenation of **3.19** using Crabtree's catalyst (5 mol%) at ambient pressure and temperature provided the fully saturated Boc-protected amino acid ester **3.20** in 99% yield as a 2:1 mixture of diastereomers. Under identical conditions, the saturated Fmoc-

protected amino acid ester **3.22** was obtained in 95% yield as a 2.4:1 mixture of diastereomers (Scheme 3.1).

Table 3.3 Regioselective hydrogenation of coupling products.

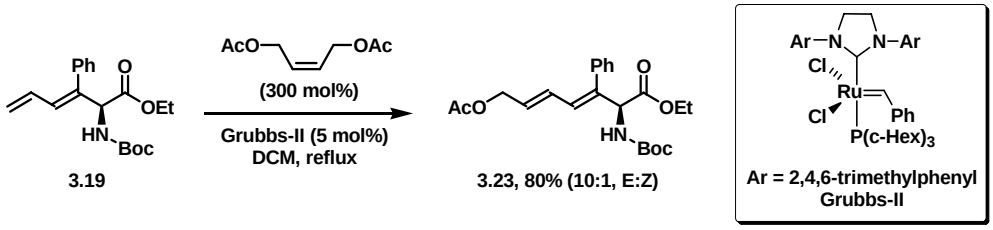




Scheme 3.1 Exhaustive hydrogenation of coupling products.

Unlike the reductive coupling of enynes with glyoxal,[1(c)] the reductive coupling of enynes with iminoacetate do not tolerate vinylic substitution. Hence, functionalization of

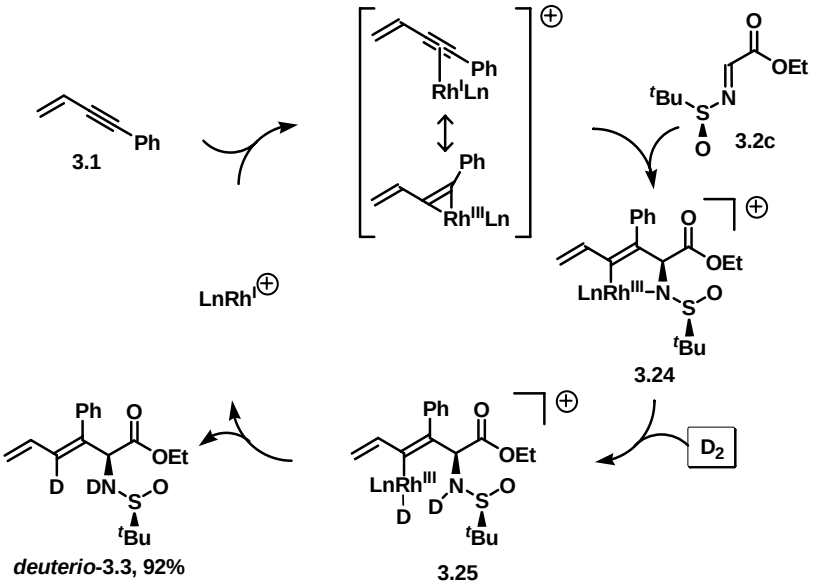
the diene terminus *via* cross-metathesis was explored. Exposure of the Boc-protected reductive coupling product **3.19** to *cis*-1,4-diacetoxy-2-butene in the presence of 5 mol% of second generation Grubbs catalyst provided the allylic acetate **3.23** in 80% yield as a 10:1 mixture of alkene stereoisomers (Scheme 3.2).



Scheme 3.2 Cross-metathesis of the coupling product **3.19**.

3.2.4 Mechanistic Studies

To gain mechanistic insight, the reductive coupling of 1,3-phenylenyne **3.1** with iminoacetate **3.2c** was performed under an atmosphere of deuterium. As expected, monodeuterated product *deuterio*-**3.3** was observed by ^{1}H-NMR. These results are consistent with a catalytic mechanism involving alkyne-imine oxidative coupling followed by hydrogenolytic cleavage of the resulting metallacycle. Based on the deuterium labeling study, a plausible mechanism was proposed. The catalytic cycle is initiated by oxidative coupling of the alkyne and imine to form metallacycle intermediate **3.24**. The following step incorporates deuterium *via* σ-bond metathesis[7] to generate the intermediate **3.25**. Finally, alkenyl rhodium monohydride complex **3.25** undergoes C-D reductive elimination to complete the catalytic cycle (Scheme 3.3).



Scheme 3.3 Plausible catalytic cycle.

Given the observed sense of stereoinduction, two stereochemical models **A** and **B** are proposed. In each case, the iminoacetate is bound to rhodium(I) in a five-membered chelate. This type of chelating model has been established for late transition metal complexes with α-iminoketones and α-iminoesters.[8] Upon oxidative coupling, the alkyne is delivered to the less hindered π-face of the imine. This is the opposite face of the bulky *tert*-butyl group in its most stable *s-cis* conformation.[9] The resulting metallacycle **C** possesses a unoccupied coordinate site **L**, which should facilitate subsequent hydrogen activation (Figure 3.2).

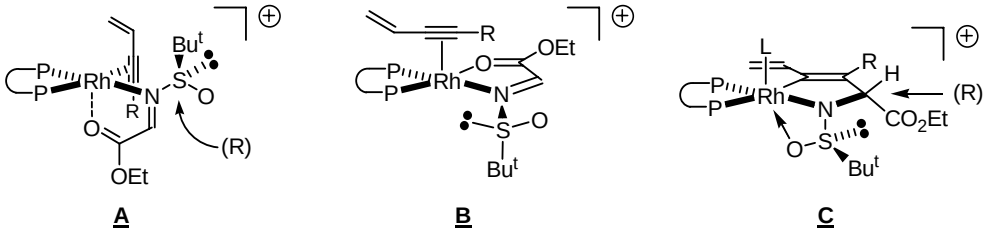


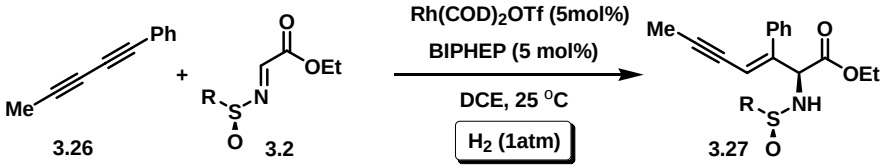
Figure 3.2 Proposed models for asymmetric induction.

3.3 REDUCTIVE COUPLING OF 1,3-DIYNES WITH IMINOACETATES

3.3.1 Optimization

The hydrogen-mediated reductive coupling of 1,3-diynes to (*N*-sulfinyl) imino-acetates was explored next. Interestingly, under conditions established for the reductive coupling of enynes, coupling of diyne **3.26** (200 mol%) to ethyl (*N*-*tert*-butanesulfinyl) iminoacetate **3.2c** did not produce the desired reductive coupling product. It was suspected that the diminished electrophilicity of the alkyl substituted sulfinyl imine decreased the reactivity of the reductive coupling. In contrast, hydrogenation of diyne **3.26** in the presence of ethyl (*N*-*para*-toluenesulfinyl) iminoacetate **3.2a** delivered the desired product **3.27a** in 94% yield as a 1.2:1 mixture of diastereomers. Remarkably, the use of the corresponding mesityl derivative **3.2b** provided the coupling product **3.27b** in 94% yield with >95:5 regio- and diastereoslectivity. Additionally, comparable results were obtained using ethyl *N*-(2,4,6-triisopropylbenzenesulfinyl) iminoacetate **3.2d**,[10] which was chosen as the standard coupling partner due to its enhanced chromatographic stability and ease of purification (Table 3.4).

Table 3.4 Optimization table.

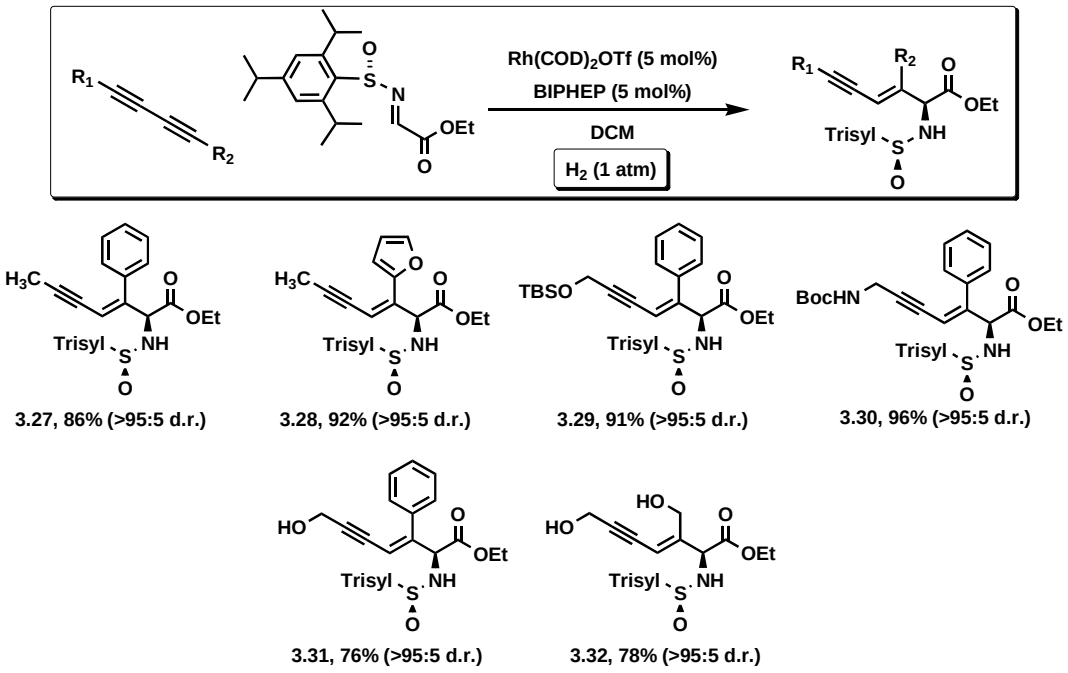


entry	R	yield (%)	dr
1	tert-Butyl (3.2c)	No Reaction	NA
2	Tolyl (3.2a)	94 (3.27a)	1.2:1
3	Mesityl (3.2b)	96 (3.27b)	>95:5
4	2,4,6-triisopropylphenyl (3.2d)	86 (3.27d)	>95:5

3.3.2 Substrate Scope

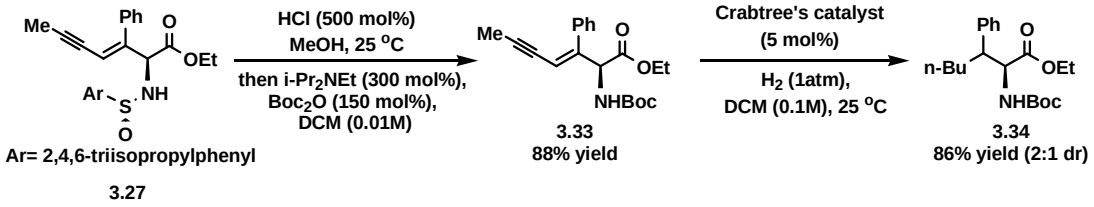
Under optimized conditions, the coupling of a variety of 1,3-diynes to ethyl *N*-(2,4,6-triisopropylbenzenesulfinyl)iminoacetate provided the enyne-containing α-amino acid ethyl esters **3.27**-**3.32** as single regio- and stereoisomers in good to excellent yield. In each case, the regioselectivity was perfect, favoring carbon-carbon bond formation proximal to the aryl substituent. The regioisomeric products, which resulted from the coupling of alkyl terminus to imine partner, were not observed. Remarkably, the unprotected diol substrate smoothly underwent the reductive coupling to provide the desired product **3.32** in good yield with excellent selectivity (Table 3.5). The stereochemical assignment of **3.27**-**3.32** was made in analogy for a derivative of enyne coupling product **3.6**, as shown in Figure 3.1.

Table 3.5 Reductive coupling of 1,3-diynes with iminoacetates.[5]



3.3.3 Elaboration of Reductive Coupling Products

The protecting group conversion was examined first. Under acidic condition, the sulfinyl protecting group was smoothly removed. Subsequent Boc protection provided the corresponding Boc-derivative **3.33** in excellent yield. Next, exhaustive hydrogenation of the Boc-derivative **3.33** using Crabtree's catalyst provided the saturated amino acid ester **3.34** in excellent yield as a 2:1 mixture of diastreomers (Scheme 3.4).



Scheme 3.4 Exhaustive Hydrogenation of compound **3.33**.

3.4 REDUCTIVE COUPLING OF 1,3-ENYNES WITH ACTIVATED KETONES

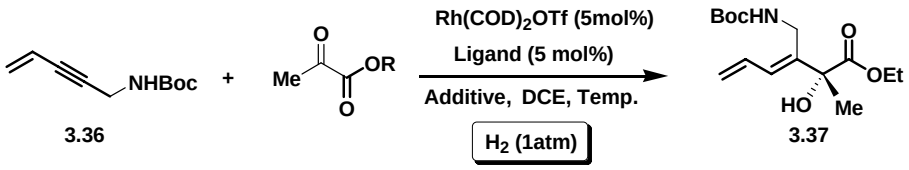
3.4.1 Introduction

The enantioselective generation of quaternary stereocenters is generally a formidable challenge. Recently, several catalytic, asymmetric methods that achieve this goal have been developed,[11] and addition reactions to ketones have attracted significant attention, as they provide access to enantiomerically enriched tertiary alcohols.[12] The Walsh group has reported highly enantioselective, catalytic addition of alkenylzirconium reagents to ketones.[13,14] However, this approach requires stoichiometric use of two metallic reagents. Here, we report that hydrogenation of conjugated enynes in the presence of α-ketoesters using a chirally modified rhodium catalyst enables formation of enantiomerically enriched tertiary alcohols.

3.4.2 Optimization

To investigate the possibility of the hydrogen-mediated reductive coupling of 1,3-enynes to ketone partners, we chose 1,3-phenylenyne and ethyl pyruvate as nucleophilic and electrophilic partner, respectively. Upon exposure of 1,3-phenylenyne to ethyl pyruvate in the presence of a cationic rhodium complex and BIPHEP ligand, the desired product **3.35** (Table 3.7) was obtained in 64% yield with high levels of stereo- and regioselectivity. This remarkable result prompted us to explore the enantioselective reductive coupling utilizing commercially available chiral bidentate phosphine ligands. For optimization of the asymmetric variant of this reaction, enyne **3.36** was adopted as the standard coupling partner due to its enhanced stability and relative ease of use (i.e. solid is easier to handle than oil). Initially, asymmetric induction was assayed under hydrogenation conditions employing $Rh(COD)_2OTf$ and (*R*)-BINAP in DCE (0.1M). The desired product **3.37** was obtained in 35% yield with 50% ee. Through an assay of commercially available chiral ligands, (*R*)-*xylyl*-WALPHOS provided excellent levels of asymmetric induction. However, chemical yields varied dramatically in response to aging of the solvent 1,2-dichloroethane (DCE). Older batches of solvent provided better results. It was reasoned that adventitious HCl might promote reductive coupling. Indeed, an assay of Brønsted acid additives revealed that reactions with substoichiometric amount of triphenylacetic acid (5 mol%) in freshly distilled DCE reproducibly gave the coupling product **3.37** in 67% yield and 78% ee. At an elevated temperature (60^oC), the coupling product was obtained in 82% yield and 89% ee. Finally, the use of methyl pyruvate instead of ethyl pyruvate provided the desired product **3.37** in 88% yield and 90% ee. In the absence of a Brønsted acid additive, but under otherwise identical conditions, the coupling product **3.37** was produced in only 42% yield and 87% ee (Table 3.6).

Table 3.6 Optimization of enantioselective reductive coupling.



entry	R	Ligand	Additive	temp (^{o}C)	yield (%)	%ee
1	Et	(R)-BINAP	None	24	35	50
2	Et	(R)-*xylyl*-WALPHOS	None	24	24	86
3	Et	(R)-*xylyl*-WALPHOS	Triphenylacetic acid	24	67	78
4	Et	(R)-*xylyl*-WALPHOS	Triphenylacetic acid	60	82	89
5	Me	(R)-*xylyl*-WALPHOS	Triphenylacetic acid	60	88	90

3.4.3 Substrate Scope

The optimized conditions were applied to the reductive coupling of a variety of conjugated enynes to methyl or ethyl pyruvate. Aryl substituted enynes underwent reductive coupling to produce the corresponding products **3.35** and **3.39** in excellent yields with high enantioselectivities. Alkyl substituted enynes also smoothly participated in the reductive coupling to give the coupling products **3.37**-**3.38** and **3.40**-**3.42**. When an unprotected propargylic alcohol derivative was employed, the lactone product **3.40** was obtained in 80% yield and 91% ee. Interestingly, in the case of alkyl substituted enynes, coupling with methyl pyruvate gave a little higher asymmetric induction than with ethyl pyruvate (Table 3.7).

To further broaden the asymmetric reductive coupling of enynes and activated ketones, a variety of α-ketoesters were investigated. Gratifyingly, the coupling of enyne with several different activated ketones afforded the corresponding products **3.43**-**3.46** in good to excellent yields and enantiomeric excesses. In all cases, the diene containing

coupling products are not subject to over-reduction under the standard conditions, and the the trisubstituted alkene is formed as a single geometrical isomer (Table 3.8).

Table 3.7 Reductive coupling of 1,3-enynes with methyl or ethyl pyruvate.[15]

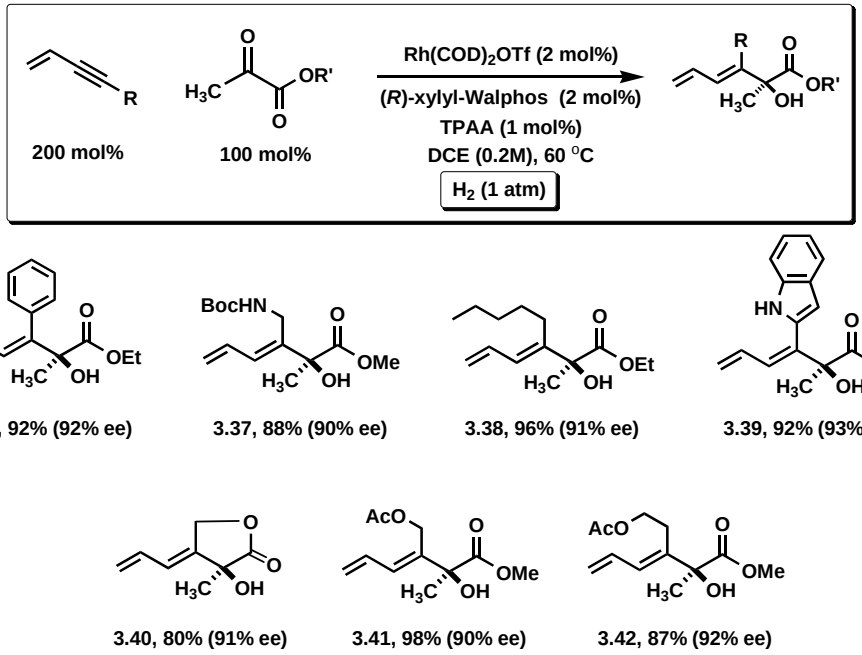
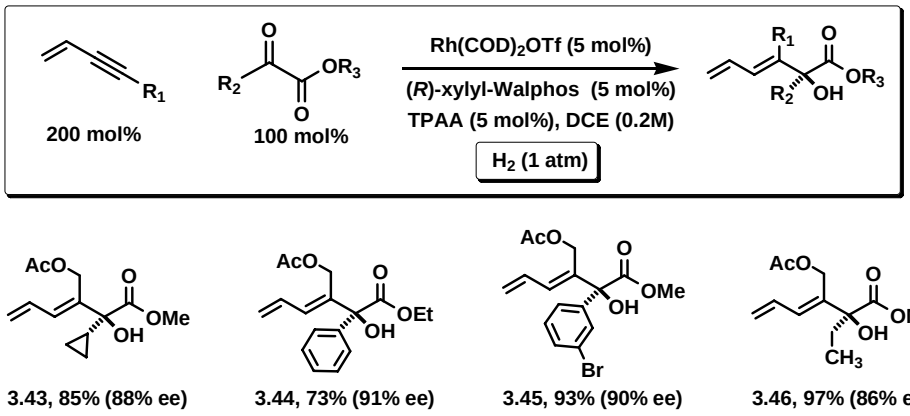
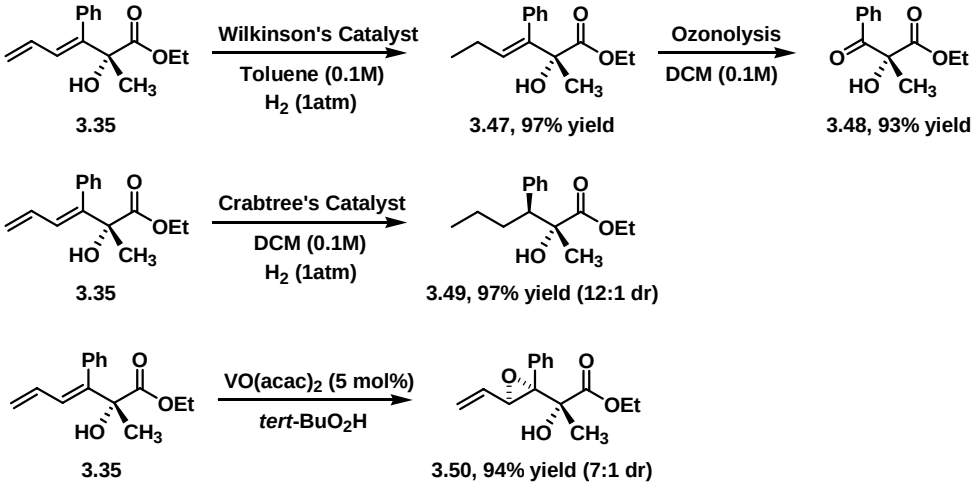


Table 3.8 Reductive coupling of the enyne with a set of α-ketoesters.



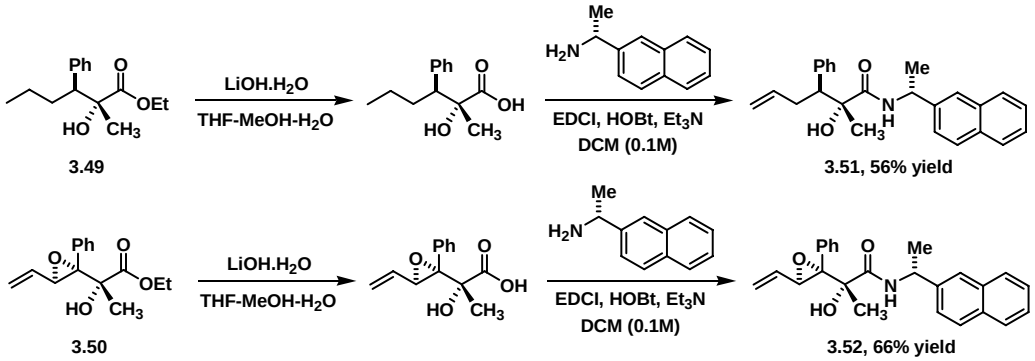
3.4.4 Elaboration of Reductive Coupling Products

In a preliminary effort to explore further manipulation of the coupling products, compound **3.35** was exposed to $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst) at ambient pressure and temperature. In the event, regioselective hydrogenation of the terminal alkene occurred cleanly to afford the β,γ-unsaturated α-hydroxy ester **3.47** in 97% yield. Ozonoloysis of compound **3.47** provided compound **3.48** in 93% yield. Next, exhaustive hydrogenation of compound **3.35** using Crabtree's catalyst provided the saturated α-hydroxy ester **3.49** in excellent yield as a 12:1 mixture of diastereomers. It was assumed that the high diastereoselective hydrogenation of compound **3.35** resulted from a directing effect by the hydroxy functional group during hydrogenation using Crabtree's catalyst.[16] To further investigate the hydroxyl group directing effect, we explored directed metal-catalyzed epoxidation. Upon exposure of the reductive coupling product **3.35** in the presence of $VO(acac)_2$ and *tert*-BuO_2H, the epoxide **3.50** was obtained in 94% yield as a 7:1 mixture of diastereomers (Scheme 3.5).



Scheme 3.5 Elaboration of reductive coupling products.

To determine the absolute and relative stereochemistry, the compound **3.49** and **3.50** were converted to amide compounds **3.51** and **3.52**, respectively (Scheme 3.6). The absolute and relative stereochemical assignment was determined by X-ray diffraction analysis of compounds **3.51** and **3.52** (Scheme 3.6).



Scheme 3.6 Preparation of amide **3.51** and **3.52** for X-ray analysis.

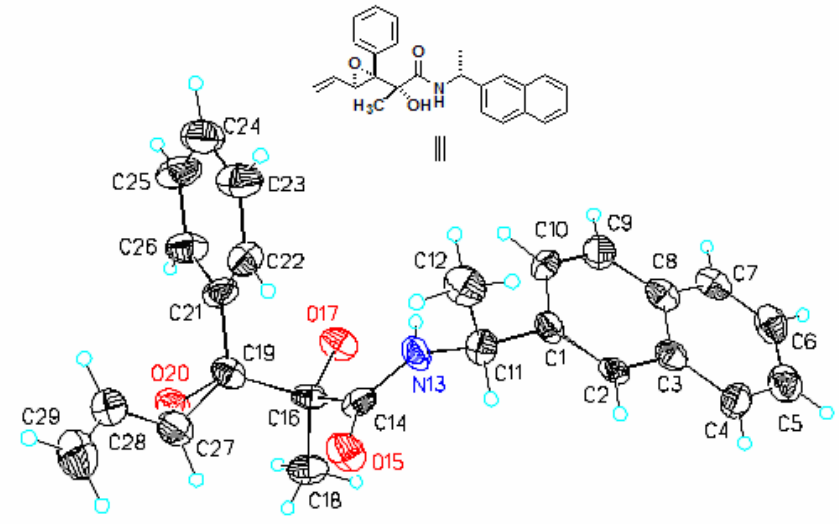
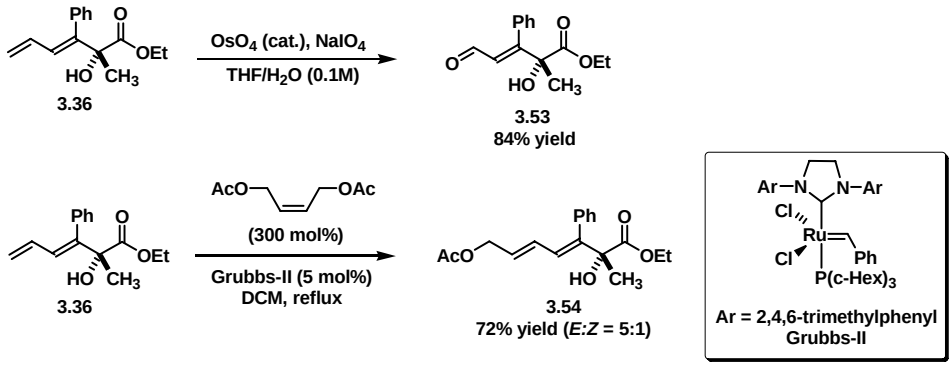


Figure 3.3 A single crystal X-ray structure of **3.52**.

Additionally, site selective oxidative cleavage of compound **3.35** under Johnson-Lemieux conditions[17] provided aldehyde **3.53** in 84% yield without isomerization of alkene geometry. Finally, functionalization of the diene terminus via cross-metathesis was explored. Exposure of the reductive coupling product **3.35** to *cis*-1,4-diacetoxy-2-butene in the presence of 5 mol% of the second generation Grubbs' catalyst provided the allylic acetate **3.54** in 72% yield as a 5:1 mixture of alkene stereoisomers (Scheme 3.7).

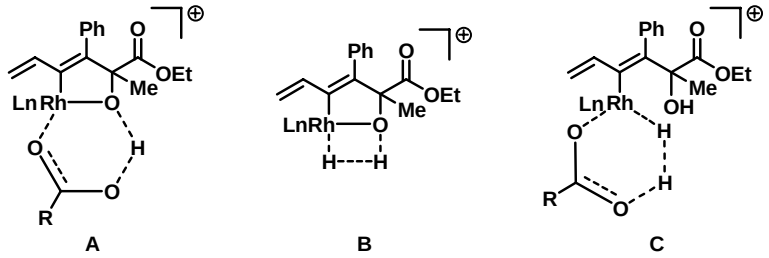


Scheme 3.7 Functionalization of compound **3.35**.

3.4.5 Mechanistic Studies

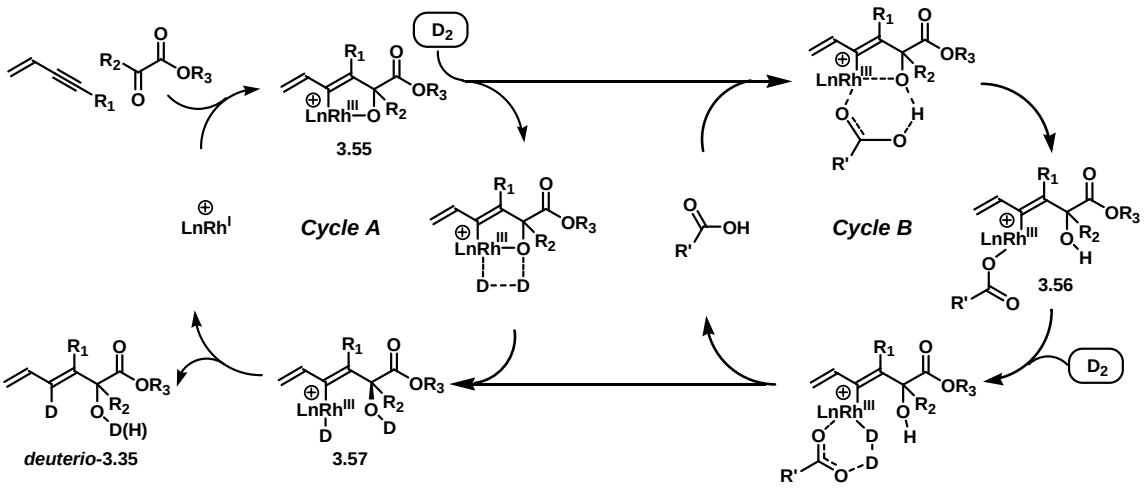
To gain insight into the role of the Brønsted acid co-catalyst, the reductive coupling of 1,3-phenylenyne and ethyl pyruvate was performed under a deuterium atmosphere to provide *deuterio*-**3.35**. This result is consistent with a catalytic mechanism involving oxidative coupling followed by hydrogenolytic cleavage of the resulting metallacycle *via* σ-bond metathesis. Even when a 50 mol% loading of Brønsted acid is used under otherwise standard conditions, with a 2 mol% loading of rhodium catalyst, clean monodeuteration persists. This result excludes mechanisms involving protonolytic cleavage of the rhodium-carbon bond of the oxametallacycle and suggests a plausible role for the acid additive might involve protonolytic cleavage of the rhodium-oxygen bond of

the oxametallacycle. Indeed, the protonolytic cleavage of the rhodium-oxygen bond in protic media (i.e. H_2O) has been studied by Hartwig.[18] Protonolysis may occur through six-membered transition state (**A**). Recent studies by Musashi and Sakaki[19] suggest that Brønsted acid cocatalysts may accelerate the reductive coupling by circumventing four-centered transition structures for σ-bond metathesis. High energy structure, (**B**) obtained by direct hydrogenolysis of the putative oxametallacyclic intermediateis compared to six-centered transition structure (**C**) from hydrogenolysis of rhodium carboxylates derived upon protonolysis of the oxametallacycle (Scheme 3.8)



Scheme 3.8 Proposed models accounting the role of Brønsted acid cocatalyst.

Based on deuterium labeling studies and other experimental data, a plausible catalytic mechanism was proposed. Without acid cocatalyst, **Cycle A** will be operative resulting in a relatively slower reaction. With acid cocatalyst, **Cycle B** will be operative. In **Cycle B**, oxidative coupling of enyne to ethyl pyruvate furnishes an oxametallacyclic intermediate **3.55**, which is protonolytically cleaved by the Brønsted acid cocatalyst to produce a cationic rhodium carboxylate **3.56**. Hydrogenolysis of the Rh-O bond followed by C-D reductive elimination of intermediate **3.57** delivers *deuterio*-**3.35**, along with the starting cationic rhodium complex to close the catalytic cycle (Scheme 3.9).



Scheme 3.9 Plausible catalytic cycle.

3.5 SUMMARY AND CONCLUDING REMARKS

The reductive coupling of conjugated alkynes and iminoacetates has been achieved through catalytic hydrogenation, representing the first use of imines as electrophilic partners in simple hydrometallative reductive coupling. Good to excellent yields and exceptional levels of regiocontrol are observed. Moreover, the high levels of relative stereocontrol with respect to the *N*-sulfinyl moiety allow the absolute stereochemical course of the reductive coupling to be controlled. The requirement of π-unsaturated reactants in the form of activated imines and conjugated alkynes suggests a weakly nucleophilic metallocyclopropane is formed through alkyne coordination with low valent rhodium. For low valent late transition metals, this pattern of reactivity may represent a driving force that assists the oxidative coupling of alkyne to C=O π-bonds.

The reductive coupling of 1,3-enynes and α-ketoesters has been achieved under rhodium-catalyzed hydrogenation conditions. This transformation is highly regioselective and affords synthetically useful 1,3-dienes with an adjacent quaternary carbinol stereogenic center in high enantioselectivity. Moreover, during the optimization of this reaction, we observed that Brønsted acid cocatalysts played a critical role in the reaction. This acid effect could be applicable to more challenging catalytic hydrogen-mediated carbon-carbon bond formations.

3.6 EXPERIMENTAL SECTION

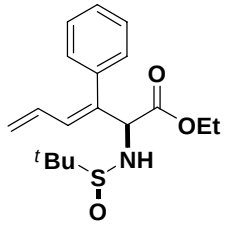
3.6.1 GENERAL

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. Dichloromethane (DCM) was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M + 1) or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian Gemini (400 MHz or 300MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (pip) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

3.6.2 Hydrogen-Mediated Reductive coupling of 1,3-Enynes and Iminoacetes

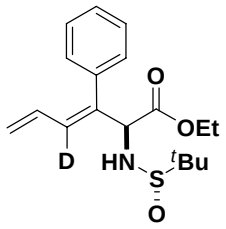
Representative Procedure for the Coupling of 1,3-phenyl enyne and *N*-(*tert*-Butane sulfinyl) iminoacetate.

To a solution of *N*-(*tert*-Butanesulfinyl)iminoacetate **3.2c** (41 mg, 0.20 mmol, 100 mol%) and 3-buten-1-ynyl-benzene **3.1** (50.9 mg, 0.40 mmol, 200 mol%) in DCM (0.67 mL, 0.3M) at 35 ^{o}C was added $Rh(COD)_2OTf$ (4.7 mg, 0.01 mmol, 5 mol%) and BIPHEP (5.3 mg, 0.01 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at 35 ^{o}C under 1 atm of hydrogen for 8 hours. The title compound was purified by flash silical chromatography (Rf = 0.3, 25% EtOAc/hexane) to afford 66.3 mg as a colorless oil (99% yield).



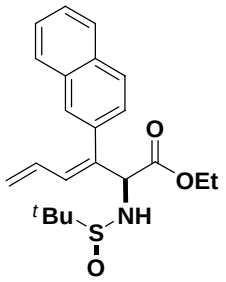
3.3

2-(2-methyl-propane-2-sulfinylamino)-3-phenyl-hexa -3,5-dienoic acid ethyl ester (3.3). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 - 7.26 (m, 3H), 7.19 - 7.16 (m, 2H), 6.42 (d, *J* = 10.8 Hz, 1H), 6.30 (dt, *J* = 16.8, 10.4 Hz, 1H), 5.15 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.14 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.80 (d, *J* = 4.0 Hz, 1H), 4.34 (d, *J* = 4.0, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 1.19 (s, 9H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 137.9, 137.0, 133.3, 132.6, 129.3, 128.0, 127.6, 120.1, 62.8, 62.0, 55.9, 22.5, 13.9. HRMS Calcd. for $C_{18}H_{26}N_1O_3S_1$ (M+1): 336.1633, Found: 336.1632. FTIR (neat): 3285, 3072, 2980, 1738, 1602, 1494, 1474, 1444, 1366, 1296, 1256, 1219, 1184, 1076, 914, 851, 776 cm^{-1}.



***deuterio*-3.3**

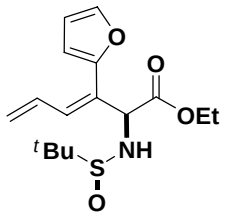
***deuterio*-2-(2-methyl-propane-2-sulfinylamino)-3-phenyl-hexa-3,5-dienoic acid ethyl ester (*deuterio*-3.3).** Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 - 7.25 (m, 3H), 7.18 - 7.15 (m, 2H), 6.29 (dd, *J* = 16.8, 10.0 Hz, 1H), 5.35 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.79 (d, *J* = 4.8 Hz, 1H), 4.34 (d, *J* = 4.4, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.17 (s, 9H), 1.17 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 137.8, 137.0, 133.2, 129.3, 128.0, 127.6, 120.1, 62.8, 62.1, 55.9, 22.5, 13.9. HRMS Calcd. for $C_{18}H_{25}D_1N_1O_3S_1$ (M+1): 337.1696, Found: 337.1692. FTIR (neat): 3285, 3056, 2980, 2870, 1732, 1601, 1493, 1473, 1444, 1412, 1391, 1366, 1253, 1220, 1074, 911, 852, 735, 703, cm^{-1}.



3.4

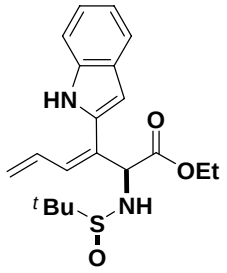
2-(2-methyl-propane-2-sulfinylamino)-3-naphthalen-2-yl-hexa-3,5-dienoic acid ethyl ester (3.4). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.84 - 7.78 (m, 3H), 7.66 (s, 1H), 7.51 - 7.46 (m, 2H), 7.30 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.51 (d, *J*

= 11.2 Hz, 2H), 6.35 (t, *J* = 10.4 Hz, 1H), 6.51 (d, *J* = 11.2 Hz, 1H), 6.30 (dt, *J* = 17.2, 10.4 Hz, 1H), 5.40 (dd, *J* = 16.8, 1.4 Hz, 1H), 5.16 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.90 (d, *J* = 4.4 Hz, 1H), 4.41 (d, *J* = 4.0, 1H), 4.20 - 4.15 (m, 2H), 1.19 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 137.9, 134.5, 133.3, 133.0, 132.9, 132.6, 128.5, 127.9, 127.6, 127.2, 126.2, 126.2, 120.3, 62.8, 62.1, 56.0, 22.5, 14.0. HRMS Calcd. for $C_{22}H_{28}N_1O_3S_1$ (M+1): 386.1790, Found: 386.1786. FTIR (neat): 3283, 2979, 1733, 1473, 1366, 1258, 1219, 1184, 1075, 914, 859, 824, 751 cm^{-1}.



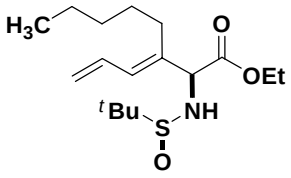
3.5

2-(2-methyl-propane-2-sulfinylamino)-3-furan-2-yl-hexa-3,5-dienoic acid ethyl ester (3.5). Rf = 0.3, 30% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, *J* = 1.2, 1H), 7.12 (dt, *J* = 17.6, 10.7, 1H), 6.42 (d, *J* = 3.2 Hz, 1H), 6.40 - 6.38 (m, 1H), 6.30 (d, *J* = 11.2 Hz, 1H), 5.46 (d, *J* = 8.4 Hz, 1H), 5.36 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.80 (d, *J* = 3.2 Hz, 1H), 4.44 (d, *J* = 2.8 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.0, 150.8, 142.2, 133.4, 132.4, 125.9, 111.0, 110.8, 62.2, 61.4, 55.7, 22.4, 13.9. HRMS Calcd. for $C_{16}H_{24}N_1O_4S_1$ (M+1): 326.1426, Found: 326.1426. FTIR (neat): 3287, 2980, 1737, 1467, 1366, 1260, 1224, 1114, 1072, 1021 cm^{-1}.



3.6

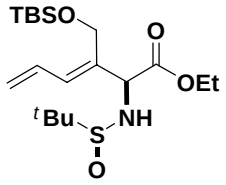
3-(1*H*-Indol-2-yl)-2-(2-methyl-propane-2-sulfinyl amino)-hexa-3,5-dienoic acid ethyl ester (3.6). Rf = 0.3, 40% EtOAc/hexane; white ^{1}H NMR (400 MHz, $CDCl_3$): 8.90 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.16 (td, *J* = 7.6, 1.1 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 1H), 6.90 (dt, *J* = 17.2, 10.6 Hz, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 6.48 (d, J = 10.8, 1H), 5.50 (d, *J* = 16.0 Hz, 1H), 5.33 (d, *J* = 10.0 Hz, 1H), 4.85 (d, *J* = 3.6, 1H), 4.46 (d, *J* = 3.2 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 1.20 (s, 9H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 136.0, 134.8, 133.4, 133.2, 127.9, 127.8, 122.5, 122.0, 120.5, 120.0, 110.9, 105.2, 62.4, 61.8, 56.0, 22.5, 13.7. HRMS Calcd. for $C_{20}H_{27}N_2O_3S_1$ (M+1): 375.1742, Found: 375.1747. FTIR (neat): 3274, 2978, 1731, 1455, 1404, 1366, 1224, 1056, 913, 850, 795, 783 cm^{-1}. MP : 50 - 52 ^{o}C



3.7

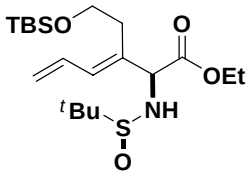
3-Allylidene-2-(2-methyl-propane-2-sulfinylamino)-octanoic acid ethyl ester (3.7). Rf = 0.4, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.58 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.11 (d, *J* = 11.2 Hz, 1H), 5.27 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.19 (dd, *J* = 9.8,

1.4 Hz, 1H), 4.45 (d, *J* = 4.0, 1H), 4.32 (d, *J* = 4.0 Hz, 1H), 4.27 -4.17 (m, 2H), 2.19 (t, *J* = 8.0, 2H), 1.44 - 1.36 (m, 2H), 1.29 - 1.26 (m, 7H), 1.26 (s, 9H), 0.88 (t, *J* = 2.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.6, 138.0, 132.1, 130.6, 118.9, 62.0, 62.0, 55.8, 31.9, 28.6, 28.6, 22.6, 22.4, 14.0, 14.0. HRMS Calcd. for $C_{17}H_{32}N_1O_3S_1$ (M+1): 330.2103, Found: 330.2090. FTIR (neat): 3452, 2956, 2869, 1734, 1465, 1365, 1255, 1182, 1078, 908, 851 cm^{-1}.



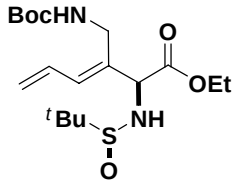
3.8

3-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(2-methyl-propane-2-sulfinylamino)-hexa-3,5-dienoic acid ethyl ester (3.8) Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.62 (dt, *J* = 16.8, 10.5 Hz, 1H), 6.13 (d, *J* = 10.8 Hz, 1H), 5.32 (dd, *J* = 15.2, 1.4 Hz, 1H), 5.24 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.59 (d, *J* = 4.4 Hz, 1H), 4.44 - 4.38 (m, 2H), 4.32 -4.23 (m, 2H), 4.17 - 4.41 (m, 1H), 1.27 (t, *J* = 1.2, 3H), 1.25 (s, 9H), 0.09 (s, 9H), 0.062 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 136.4, 131.2, 131.1, 120.3, 61.8, 60.1, 58.6, 55.8, 25.8, 22.6, 18.3, 14.0, -5.52. HRMS Calcd. for $C_{19}H_{38}N_1O_4Si_1S_1$ (M+1): 404.2291, Found: 404.2299. FTIR (neat): 3418, 2956, 2925, 2857, 1735, 1472, 1365, 1255, 1212, 1077, 838, 778, 736 cm^{-1}.



3.9

3-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-2-(2-methyl-propane-2-sulfinylamino)-hexa-3,5-dienoic acid ethyl (3.9) Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.55 (dt, *J* = 16.8, 10.6 Hz, 1H), 6.12 (d, *J* = 10.8, 2H), 5.24 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.17 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.45 (d, *J* = 4.8 Hz, 1H), 4.32 (d, *J* = 4.4, 1H), 4.25 -4.11 (m, 2H), 3.63 - 3.53 (m, 2H), 2.48 - 2.34 (m, 2H), 1.24 (t, *J* = 6.4 Hz, 3H), 1.21 (s, 9H), 0.84 (s, 9H), 0.018 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 134.1, 132.3, 132.1, 119.5, 62.4, 62.1, 62.0, 55.9, 32.2, 25.9, 22.6, 18.2, 14.0, -5.37. HRMS Calcd. for $C_{20}H_{40}N_1O_4Si_1S_1$ (M+1): 418.2447, Found: 418.2447. FTIR (neat): 3447, 3283, 2956, 2929, 2857, 1734, 1646, 1472, 1388, 1365, 1255, 1181, 1086, 989, 912, 836, 776 cm^{-1}.



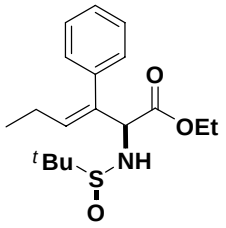
3.10

3-(*tert*-Butoxycarbonylamino-methyl)-2-(2-methyl-propane-2-sulfinylamino)-hexa-3,5-dienoic acid ethyl ester (3.10). Rf = 0.3, 30% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.67 (dt, *J* = 16.4, 10.4 Hz, 1H), 6.26 (d, *J* = 11.2 Hz, 1H), 5.39 (d, *J* = 16.4 Hz, 1H), 5.32 (d, *J* = 10.0 Hz, 1H), 4.58 (s, 1H), 4.53 (d, *J* = 3.6 Hz, 1H), 4.45 (s,

1H), 4.23 (q, J = 7.1 Hz, 2H), 3.94 (d, J =5.2 Hz, 1H), 1.43 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H), 1.27 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.9, 155.3, 134.5, 132.9, 131.1, 121.4, 79.4, 62.2, 61.2, 55.8, 37.3, 28.2, 22.5, 14.0. HRMS Calcd. for $C_{18}H_{33}N_2O_5S_1$ (M+1): 389.2110, Found: 389.2108. FTIR (neat): 3384, 2978, 1734, 1707, 1507, 1457, 1391, 1366, 1251, 1170, 1064, 917, 734 cm^{-1}.

Representative Procedure for the Selective Hydrogenation of the Diene 3.3

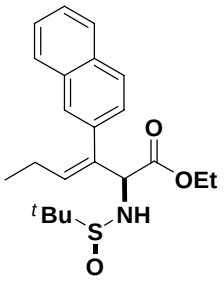
To a solution of diene **3.3** (33.5 mg, 0.1 mmol, 100 mol%) in toluene (1 mL, 0.1M) was added $RhCl(PPh_3)_3$ (9.3 mg, 0.01 mmol, 10 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 24 hours. The title compound was purified by flash silica chromatography (Rf = 0.3, 25% EtOAc/hexane) to afford 24.9 mg as a colorless oil (74% yield).



3.11

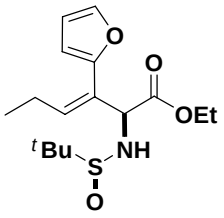
2-(2-Methyl-propane-2-sulfinylamino)-3-phenyl-hex-3-enoic acid ethyl ester (3.11). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 - 7.23 (m, 3H), 7.13 - 7.10(m, 2H), 5.83 (t, J = 7.4 Hz, 1H), 4.72 (d, J = 4.4 Hz, 2H), 4.23 (d, J = 4.0 Hz, 1H), 4.20 - 4.12 (m, 2H), 1.99 (qt, J = 7.4 Hz, 2H), 1.19 (t, J = 7.0 Hz, 3H), 1.19

(s, 9H), 0.95 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 137.3, 136.0, 135.6, 129.1, 127.9, 127.2, 63.1, 61.8, 55.8, 22.5, 22.3, 14.0, 13.9. HRMS Calcd. for $C_{18}H_{28}N_1O_3S_1$ (M+1): 338.1790, Found: 338.1792. FTIR (neat): 3279, 2964, 2930, 2871, 1735, 1458, 1365, 1295, 1254, 1214, 1183, 1076, 1022, 884, 847, 760, 702 cm^{-1}.



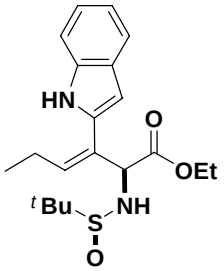
3.12

2-(2-Methyl-propane-2-sulfinylamino)-3-naphthalen-2-yl-hex-3-enoic acid ethyl ester (3.12). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.83 - 7.76 (m, 3H), 7.60 (s, 1H), 7.49 - 7.45 (m, 2H), 7.25 (d, J = 8.6, 1H), 5.90 (t, J = 7.6 Hz, 1H), 4.81 (s, 1H), 4.33 (s, 1H), 4.21 - 4.13 (m, 2H), 2.02 (qt, J = 7.5 Hz, 2H), 1.20 (s, 9H), 1.18 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 136.5, 135.6, 134.9, 133.0, 132.4, 128.0, 127.5, 127.5, 127.4, 126.0, 125.9, 63.1, 61.9, 29.6, 22.7, 22.6, 22.4, 14.0. HRMS Calcd. for $C_{22}H_{30}N_1O_3S_1$ (M+1): 388.1946, Found: 388.1953. FTIR (neat): 3285, 3054, 2961, 2870, 1734, 1597, 1503, 1458, 1365, 1181, 1075, 1019, 859, 749 cm^{-1}.



3.13

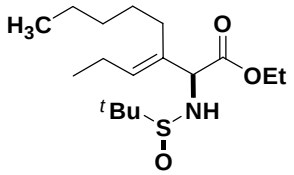
3-Furan-2-yl-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (3.13). Rf = 0.3, 30% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (t, *J* = 2.0 Hz, 1H), 6.37 - 6.36 (m, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 5.77 (t, *J* = 7.2 Hz, 1H), 4.75 (s, 1H), 4.41 (s, 1H), 4.23 - 4.15 (m, 2H), 2.42 (qt, *J* = 7.5 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.14 (s, 9H), 1.09 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.3, 150.7, 141.3, 137.4, 125.6, 110.7, 109.6, 62.0, 61.8, 29.7, 22.8, 22.4, 14.0, 13.9. HRMS Calcd. for $C_{16}H_{26}N_1O_4S_1$ (M+1): 328.1583, Found: 328.1573. FTIR (neat): 3288, 2966, 2921, 2850, 1735, 1458, 1366, 1261, 1221, 1071, 1025 cm^{-1}.



3.14

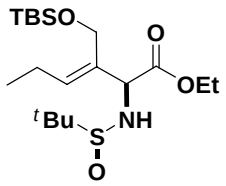
3-(1*H*-Indol-2-yl)-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (3.14). Rf = 0.3, 40% EtOAc/hexane; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.84 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.14 (td, *J* = 7.6, 1.1 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 1.2, 1H), 5.94 (t, *J* = 7.4 Hz, 1H), 4.78 (d, *J* = 3.2 Hz, 2H), 4.41 (d, *J* = 2.4 Hz, 1H), 4.14 (qd, *J* = 7.2, 1.2 Hz, 2H), 2.45 - 2.37 (m, 2H),

1.21 (s, 9H), 1.10 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.5, 140.1, 136.6, 133.4, 127.9, 126.1, 122.1, 120.3, 119.8, 110.9, 103.9, 62.3, 62.1, 55.9, 22.1, 22.6, 22.5, 14.0, 13.9. HRMS Calcd. for $C_{20}H_{29}N_2O_3S_1$ (M+1): 377.1900, Found: 377.1900. FTIR (neat): 3403, 3276, 2965, 2861, 1732, 1653, 1456, 1366, 1301, 1225, 1054 cm^{-1}. MP : 36 -38 ^{o}C.



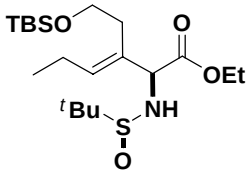
3.15

2-(2-Methyl-propane-2-sulfinylamino)-3-propylidene -octanoic acid ethyl ester (3.15). Rf = 0.4, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 5.47 (t, J = 7.2 Hz, 1H), 4.38 (d, J = 4.4 Hz, 1H), 4.25 - 4.16 (m, 1H + 2H), 2.22 – 2.01 (m, 4H), 1.37 – 1.25 (m, 6H), 1.25 (s, 9H), 0.98 (t, J = 7.6 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 134.6, 133.7, 62.3, 61.7, 55.7, 32.0, 28.3, 30.0, 22.6, 22.5, 21.3, 14.1, 14.0, 13.9. HRMS Calcd. for $C_{17}H_{34}N_1O_3S_1$ (M+1): 332.2259, Found: 332.2251. FTIR (neat): 3422, 2959, 2862, 1734, 1638, 1465, 1255, 1077 cm^{-1}.



3.16

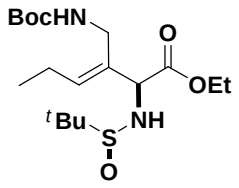
3-(tert-Butyl-dimethyl-silanyloxymethyl)-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoicacid ethyl ester (3.16). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 5.55 (t, *J* = 7.4 Hz, 1H), 4.52 (d, *J* = 4.4 Hz, 1H), 4.27 (d, *J* = 4.4 Hz, 1H), 4.29 - 4.09 (m, 2H + 2H), 2.11 (qd, J = 7.5, 2.4 Hz, 2H), 2.78 (t, *J* = 4.4 Hz, 3H), 1.25 (s, 9H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.8, 134.4, 134.2, 61.5, 60.4, 58.2, 55.6, 25.9, 22.6, 21.0, 18.3, 14.0, -5.5. HRMS Calcd. for $C_{19}H_{40}N_1O_4Si_1S_1$ (M+1): 406.2447, Found: 406.2448. FTIR (neat): 2957, 2930, 2857, 1736, 1472, 1389, 1364, 1253, 1204, 1082, 849, 777 cm^{-1}.



3.17

3-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-2-(2-methy-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (3.17). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 5.51 (t, *J* = 7.2 Hz, 1H), 4.38 (d, *J* = 5.2 Hz, 1H), 4.24 (d, *J* = 5.2 Hz, 1H), 4.22 - 4.11 (m, 2H), 3.60 - 3.48 (m, 2H), 2.36 - 2.21 (m, 2H), 2.07 (qt, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.22 (s, 9H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.9, 135.6, 130.9, 62.6, 61.9, 61.8, 55.7,

31.7, 25.9, 22.6, 21.4, 18.3, 14.0, 13.9, -5.3. HRMS Calcd. for $C_{20}H_{40}N_1O_4Si_1S_1$ (M+1): 418.2447, Found: 418.2447. FTIR (neat): 2958, 2857, 1736, 1472, 1364, 1255, 1188, 1084, 836, 776 cm^{-1}.



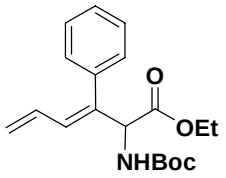
3.18

3-(tert-Butoxycarbonylamino-methyl)-2-(2-methyl-propane-2-sulfinylamino)-hex-3-enoic acid ethyl ester (3.18). Rf = 0.3, 30% EtOAc/hexane; colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 5.71 (t, *J* = 7.2 Hz, 1H), 4.55 (s, 1H), 4.46 (d, *J* = 2.8 Hz, 1H), 4.38 (s, 1H), 4.22 (q, *J* = 7.1, 2H), 3.81 (d, *J* = 5.2, 2H), 2.19 (qt, *J* = 7.6, 2H), 1.42 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 9H), 1.02 (t, *J* = 7.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 171.5, 155.4, 138.5, 130.8, 79.3, 62.2, 61.6, 55.7, 37.2, 29.7, 28.4, 22.6, 21.3, 14.0, 13.9. HRMS Calcd. for $C_{18}H_{35}N_2O_5S_1$ (M+1): 391.2267, Found: 391.2278. FTIR (neat): 3301, 2975, 2927, 1738, 1713, 1509, 1459, 1391, 1360, 1248, 1174, 1075 cm^{-1}.

Rpresentative Procedure for Desulfinylation and *N*-Protection of the Diene 3.3

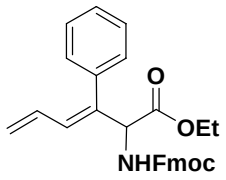
The diene **3.3** (1.14 g, 3.4 mmol, 100 mol%) was dissolved in MeOH (340 mL, 0.01M) and treated with HCl in dioxane (4.25 mL, 4.0 M in dioxane, 500 mol%). The reaction was allowed to stir at ambient temperature for 10 hours. The reaction mixture was concentrated and coevaporated with MeOH. The residue was dissolved in DCM (340

mL, 0.01M) followed by addition of DiPEA (1.8 mL, 300 mol%) and Boc_2O (1.12 g, 5.1 mmol, 150 mol%). The reaction mixture was stirred for 12 hours before diluting with DCM and H_2O. The organic phase was washed with an aqueous solution of citric acid (10 wt%), a saturated aqueous solution of $NaHCO_3$ and with H_2O. After drying (Na_2SO_4), the organic phase was evaporated *in vacuo* and the residue was purified by silica gel column chromatography (Rf = 0.5 15% EtOAc/hexane) to afford 1.07 g as a colorless oil (94% yield).



3.19

2-*tert*-Butoxycarbonylamino-3-phenyl-hexa-3,5-dienoic acid ethyl ester (3.19). Rf = 0.5 15% EtOAc/hexane; colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 7.17 – 7.26 (m, 3H), 7.17 (s, *J* = 7.2 Hz, 2H), 6.39 (d, *J* = 11.2 Hz, 1H), 6.23(dt, *J* = 16.8, 10.5 Hz, 1H), 5.34 (d, *J* = 1.6 Hz, 1H), 5.30 (d, *J* = 1.6 Hz, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 5.06 (d, *J* = 8.0 Hz, 1H), 4.14 (m, 2H), 1.43 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 154.7, 138.3, 137.0, 133.3, 131.0, 129.2, 128.2, 127.7, 119.6, 79.9, 61.6, 59.7, 28.2, 13.7. HRMS Calcd. for $C_{19}H_{26}N_1O_4$ (M+1): 332.1862, Found: 332.1862. FTIR (neat): 3439, 2978, 2933, 1740, 1717, 1492, 1367, 1323, 1248, 1162, 1058, 1026, 912, 865, 777, 704 cm^{-1}.

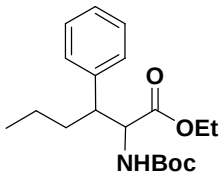


3.21

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-phenyl -hexa-3,5-dienoic acid ethyl ester (3.21). Rf = 0.3 10% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.42 – 7.29 (m, 7H), 7.20 (d, *J* = 6.8 Hz, 2H), 6.44 (d, *J* = 10.8 Hz, 1H), 6.23 (dt, *J* = 17.2, 10.5 Hz, 1H), 5.68 (d, *J* = 8.0 Hz, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.15 (d, *J* = 7.2 Hz, 1H), 5.14 (d, *J* = 10.4 Hz, 1H), 4.44 (dd, *J* = 10.2, 7.0 Hz, 1H), 4.26 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.25 – 4.17 (m, 3H), 1.21 (t, *J* = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 155.2, 143.7, 143.6, 141.2, 138.0, 136.9, 133.2, 131.2, 129.2, 128.2, 127.8, 127.6, 127.0, 125.1, 125.0, 120.0, 119.9, 67.0, 61.8, 60.0, 47.1, 14.0**. HRMS** Calcd. for $C_{29}H_{28}N_1O_4$ (M+1): 454.2018, Found: 454.2015. FTIR (neat): 3344, 2979, 1720, 1498, 1449, 1321, 1194, 1047, 912, 758, 740, 703 cm^{-1}.

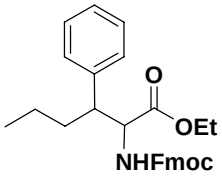
Representative Procedure for the Exhaustive Hydrogenation of Diene Products.

To a solution of diene **3.19** (44 mg, 0.13 mmol, 100 mol%) in DCM (1.3 mL, 0.1M) at ambient temperature was added Ir(COD)(Pyr)[P(*c*-Hex)$_3$]PF_6 (5.2 mg, 0.03 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 24 hours. The title compound was purified by flash silica chromatography (Rf = 0.6, 15% EtOAc/hexane) to afford 38.4 mg of **3.20** as a colorless oil (86% yield, 2:1 dr).



3.20

2-*tert*-Butoxycarbonylamino-3-phenyl-hexanoic acid ethyl ester (3.20). Rf = 0.4, 10% EtOAc/hexane; colorless oil; ^{1}H NMR (300MHz, $CDCl_3$); Major: 7.33 -7.24 (m, 3H), 7.18 – 7.15 (m, 2H), 5.06 (d, *J* = 9.3 Hz, 1H), 4.47 (t, *J* = 8.1 Hz, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 2.93 (q, *J* = 7.4 Hz, 1H), 1.78 (q, *J* = 7.5 Hz, 2H), 1.45 (s, 9H), 1.27 – 1.12 (m, 2H), 1.05 (t, *J* = 7.0, 3H), 0.87 (t, *J* = 7.4 Hz, 3H); Minor: 7.30 -7.11 (m, 3H), 7.11 – 7.09 (m, 2H), 4.77 (d, *J* = 8.7 Hz, 1H), 4.55 (dd, *J* = 9.3, 5.1 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.16 (dd, *J* = 16.2, 7.5 Hz, 1H), 1.72 (q, *J* = 7.9 Hz, 2H), 1.39 (s, 9H), 1.24 – 1.19 (m, 5H), 0.85 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100MHz, $CDCl_3$); Major: 171.8, 155.2, 139.9, 128.4, 128.3, 127.0, 79.8, 60.9, 58.4, 49.1, 33.3, 28.3, 20.5, 13.9, 13.8. HRMS Calcd. for $C_{19}H_{30}N_1O_4$ (M+1): 336.2175, Found: 336.2175. FTIR (mixture, neat): 3442, 3558, 2960, 2932, 2871, 1718, 1496, 1454, 1391, 1367, 1340, 1253, 1171, 1048, 1026, 863, 776, 757, 701 cm^{-1}.

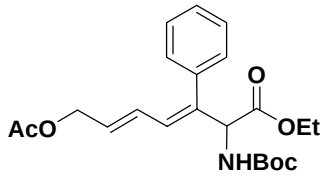


3.22

2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-phenyl -hexanoic acid ethyl ester (3.22). Rf = 0.2, 10% EtOAc/hexane; colorless oil; ^{1}H NMR (400MHz, $CDCl_3$); Major: 7.78 (d, *J* = 7.6 Hz,2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.42(t, *J* = 7.6 Hz, 2H), 7.35 – 7.24 (m, 5H), 7.14 (d, *J* = 7.6 Hz, 2H), 5.33 (d, *J* = 9.2 Hz, 1H), 4.55 (t, *J* = 8.2 Hz, 1H), 4.47 (dd,

J = 10.4, 7.2 Hz, 1H), 4.36 (dd, *J* = 10.4, 7.2 Hz, 1H), 4.23 (t, *J* = 6.8 Hz, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 2.96 (q, *J* = 7.3 Hz, 1H), 1.80 (q, *J* = 7.6 Hz, 2H), 1.24 – 1.15 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); Minor: 7.77 (d, *J* = 7.6 Hz,2H), 7.56 (t, *J* = 8.4 Hz, 2H), 7.41(td, *J* = 7.3, 1.9 Hz, 2H), 7.34 – 7.24 (m, 5H), 7.10 (d, *J* = 6.8 Hz, 2H), 5.04 (d, *J* = 9.6 Hz, 1H), 4.66 (q *J* = 4.7 Hz, 1H), 4.45 (dd, *J* = 10.8, 7.2 Hz, 1H), 4.34 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 1H), 4.15 (q, *J* = 7.2 Hz, 2H), 3.23 (q, *J* = 9.8 Hz, 1H), 1.73 (q, *J* = 11.4 Hz, 2H), 1.30 – 1.22 (m, 2H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$); Major: 171.4, 155.7, 143.9, 143.7, 141.3, 139.5, 128.4, 128.3, 127.7, 127.1, 127.0, 125.1, 125.0, 119.9, 66.9, 61.1, 58.8, 49.1, 47.2, 33.2, 20.5, 13.9, 13.8. HRMS Calcd. for $C_{29}H_{32}N_1O_4$ (M+1): 458.2331, Found: 458.2336. FTIR (mixture, neat): 3442, 3558, 2960, 2932, 2871, 1718, 1496, 1454, 1391, 1367, 1340, 1253, 1171, 1048, 1026, 863, 776, 757, 701 cm^{-1}.

Procedure for Cross-Metathesis Reaction of Diene product 3.19 with 1,4-Diacetoxy-cis-2-butene.



3.23
(mixture of two diastereomers)

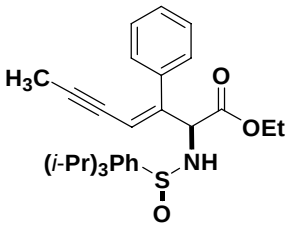
To a solution of Grubbs' catalyst (17.6 mg, 0.021 mmol, 5 mol%) in DCM (2.2 mL, 0.2 M) was added diene **3.19** (139.4 mg, 0.416 mmol, 100 mol%) and 1,4-diacetoxy-*cis*-2-butene (215.0 mg, 1.248 mmol, 300 mol%), and the solution stirred for 12 hours at 40 °C. The volatiles were removed by rotary evaporation, and the residue was purified by silica flash chromatography (Rf = 0.4, 20% EtOAc/hexane) to afford 57.8 mg as a

colorless oil (80% yield, *E:Z* = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): 7.35 – 7.30 (m, 3H), 7.15 d, *J* = 6.8 Hz, 2H), 6.63 and 6.37 (minor: d, *J* = 11.6 Hz, major: d, *J* = 10.8 Hz, 1H), 6.12 and 6.01 (major: t, *J* = 13.0 Hz, minor: t, *J* = 11.6 Hz, 1H), 5.85 and 5.53 – 5.47 (major: dt, *J* = 15.2, 6.4 Hz, minor: m, 1H), 5.33 and 5.13 (major: d, *J* = 7.2 Hz, minor: m, 1H), 5.03 and 4.89 (major: d, *J* =7.6 Hz, minor: m, 1H), 4.77 and 4.48 (minor: d, *J* = 6.8 Hz, major: d, *J* = 6.0 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.06 and 1.99 (minor: s, major: s, 3H), 1.41 (s, 9H), 1.16 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): ^{13}C NMR (100 MHz, $CDCl_3$) Major: 190.6, 154.6, 139.4, 136.7, 130.4, 129.3, 129.2, 129.1, 129.0, 128.2, 127.8, 79.9, 64.6, 61.7, 59.7, 28.2, 20.8, 13.9. HRMS Calcd. for $C_{22}H_{30}N_1O_6$ (M+1): 404.2073, Found: 404.2069. FTIR (neat): 3375, 3374, 2978, 2923, 1741, 1715, 1493, 1368, 1325, 1230, 1161, 1056, 1025, 976, 865, 777, 704.

3.6.3 Reducitve Coupling of 1,3-Diynes and Iminoacetates

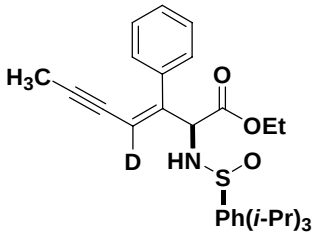
Representative Procedure for the Coupling of 1,3-Diyne 3.26 and *N*-(2,4,6-triisopropyl) benzenesulfinyl iminoacetate

To a solution of *N*-(2,4,6-triisopropyl)benzenesulfinyl iminoacetate (70.3 mg, 0.2 mmol, 100 mol%) and 1,3-diyne **3.26** (56.1 mg, 0.4 mmol, 200 mol%) in DCM (2 mL, 0.1M) at ambient temperature was added $Rh(COD)_2OTf$ (4.7 mg, 0.01 mmol, 5 mol%) and BIPHEP (5.3 mg, 0.01 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 1 hour. The title compound was purified by flash silica chromatography (Rf = 0.25, 15% EtOAc/hexane) to afford 85.1 mg as a colorless oil (86% yield).



3.27

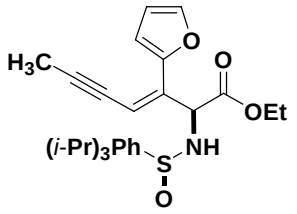
3-Phenyl-2-(2,4,6-triisopropyl-benzenesulfinylamino) -hept-3-en-5-ynoic acid ethyl ester (3.27). Rf = 0.25, 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 – 7.41 (m, 2H), 7.33 – 7.27 (m, 3H), 7.02 (s, 2H), 5.88 (qd, *J* = 2.4, 0.4 Hz, 1H), 4.94 (d, *J* = 8.0 Hz, 1H), 4.80 (d, *J* = 8.4 Hz, 1H), 4.19 – 4.08 (m, 2H), 3.92 (s,2H), 2.84 (qt, *J* = 6.9 Hz, 1H), 1.82 (d, *J* = 2.4, 3H), 1.20 (d, *J* = 6.8, 6H), 1.18 (d, *J* = 6.8 Hz, 12H), 1.63 (t, *J* = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 152.1, 148.0, 146.3, 137.4, 136.5, 128.6, 128.1, 128.0, 122.9, 111.9, 91.9, 62.8, 61.8, 34.3, 28.1, 24.3, 24.1, 23.7, 23.7, 13.9, 4.5. HRMS Calcd. for $C_{30}H_{40}N_1O_3S_1$ (M+1): 494. 2729, Found: 494.2736. FTIR (neat): 2961, 2928, 2868, 1738, 1597, 1463, 1383, 1363, 1259, 1190, 1093, 1027 cm^{-1}.



***deuterio*-3.27**

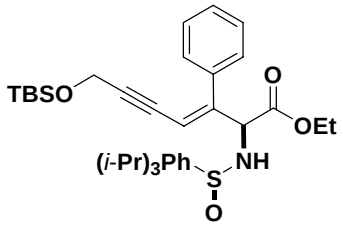
***deuterio*-3-Phenyl-2-(2,4,6-triisopropylbenzenesulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (*deuterio* -3.27).** Rf = 0.25, 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.45 – 7.43 (m, 2H), 7.34 – 7.28 (m, 3H), 7.03 (s, 2H), 4.96 (d, *J* = 8.0 Hz, 1H), 4.81 (d, *J* = 8.0 Hz, 1H), 4.19 – 4.09 (m, 2H), 3.92 (br, 2H), 2.89 – 2.82 (m, 1H), 1.83 (s, 3H), 1.25 – 1.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.8, 152.0, 148.0,

146.1, 137.3, 136.4, 128.5, 128.1, 128.0, 122.9, 91.8, 62.7, 61.8, 34.2, 28.1, 24.2, 24.1, 23.7, 13.9, 4.5. HRMS Calcd. for $C_{30}H_{39}D_1N_1O_3S_1$ (M+1): 495. 2792, Found: 495.2785. FTIR (neat): 2960, 2868, 1739, 1597, 1462, 1363, 1257, 1189, 1094, 1027, 879, 697 cm^{-1}.



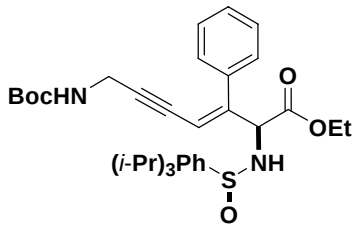
3.28

3-Furan-2-yl-2-(2,4,6-triisopropyl-benzenesulfinyl amino)-hept-3-en-5-ynoic acid ethyl ester (3.28). Rf = 0.25, 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.29 (d, *J* = 2.0, 1H), 7.21 (d, *J* = 3.2, 1H), 7.05 (s, 2H), 6.44 (q, *J* = 1.7, 1H), 5.68 (q, *J* = 2.7, 1H), 5.21 (d, *J* = 9.2 Hz, 1H), 4.93 (d, *J* = 9.2 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.96 (s, 2H), 2.87 (qt, *J* = 6.9 Hz, 1H), 2.09 (d, *J* = 2.8, 3H), 1.24 – 1.19 (m, 18H), 1.14 (t, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 151.9, 150.8, 147.9, 141.4, 137.9, 135.4, 122.9, 111.7, 111.3, 107.9, 96.4, 78.1, 61.9, 61.8, 34.3, 28.2, 24.3, 24.1, 23.8, 23.7, 13.9, 4.94. HRMS Calcd. for $C_{28}H_{38}N_1O_4S_1$ (M+1): 484. 2522, Found: 484.2504. FTIR (neat): 2960, 2868, 1741, 1597, 1565, 1463, 1384, 1364, 1261, 1194, 1093, 1016, 880, 842, 746 cm^{-1}.



3.29

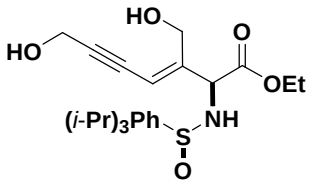
7-(tert-Butyl-dimethyl-silanyloxy)-3-phenyl-2-(2,4,6-triisopropyl-benzenesulfinyl-amino)-hept-3-en-5-ynoic acid ethyl ester (3.29). Rf = 0.3, 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 – 7.37 (m, 2H), 7.32 – 7.26 (m, 3H), 7.02 (s, 2H), 5.94 (t, *J* = 1.0 Hz, 1H), 4.95 (d, *J* = 8.8 Hz, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 4.28 (d, *J* = 2.0 Hz, 2H), 4.16 – 4.10 (m, 2H), 3.91 (s,2H), 2.84 (qt, *J* = 7.0 Hz, 1H), 1.20 (d, *J* = 7.2, 6H), 1.17 (d, *J* = 6.8 Hz, 12H), 1.16 (t, *J* = 7.2, 3H), 0.83 (s, 9H), -0.017 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.6, 152.1, 148.1, 148.0, 137.3, 136.2, 128.6, 128.3, 128.1, 123.0, 111.0, 93.2, 81.6, 62.8, 61.9, 52.1, 34.3, 28.1, 25.7, 24.3, 24.1, 23.7, 18.2, 13.9, -5.31. HRMS Calcd. for $C_{36}H_{54}N_1O_4Si_1S_1$ (M+1): 624.3543, Found: 624.3534. FTIR (neat): 2958, 2928, 2857, 1739, 1597, 1566, 1495, 1462, 1444, 1364, 1301, 1256, 1188, 1087, 938, 878, 837, 778, 698, 653 cm^{-1}.



3.30

7-tert-Butoxycarbonylamino-3-phenyl-2-(2,4,6-tri-isopropyl-benzenesulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (3.30). Rf = 0.3, 25% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 – 7.37 (m, 2H), 7.38 – 7.27 (m, 3H), 7.02 (s, 2H), 5.90 (d, *J* = 0.8 Hz, 1H), 4.94 (d, *J* = 8.4 Hz, 1H), 4.82 (d, *J* = 8.4 Hz, 1H), 4. 49 (s, 1H), 4.19 – 4.07 (m, 2H), 3.90 – 3.88 (m, 4H), 2.84 (qt, *J* = 6.9 Hz, 1H), 1.40 (s, 9H), 1.21 (d, *J* = 7.2, 6H), 1.17 (dd, *J* = 6.8, 2.0 Hz, 12H), 1.15 (t, *J* = 7.2, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 155.1, 152.1, 148.4, 148.1, 137.3, 136.2, 128.5, 128.4, 128.1, 123.0,

110.8, 90.9, 80.2, 79.8, 62.9, 62.0, 34.3, 31.2, 28.3, 28.2, 24.3, 24.1, 23.7, 23.7, 13.9. HRMS Calcd. for $C_{35}H_{48}N_2O_5S_1$ (M): 608.3284, Found: 608.3283. FTIR (neat): 2961, 2869, 1738, 1598, 1566, 1463, 1443, 1425, 1384, 1364, 1260, 1191, 1094, 1027, 938, 770, 736, 698 cm^{-1}.



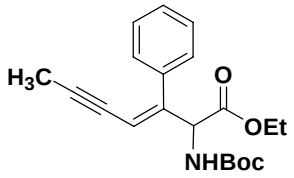
3.32

7-Hydroxy-3-hydroxymethyl-2-(2,4,6-triisopropyl-benzenesulfinylamino)-hept-3-en-5-ynoic acid ethyl ester (3.32). Rf = 0.2, 30% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.06 (s, 2H), 5.72 (s, 1H), 5.32 (d, *J* = 8.4 Hz, 1H), 4.75 (d, *J* = 8.4 Hz, 1H), 4.59 (d, *J* = 14.4 Hz, 1H), 4.45 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 0.8 Hz, 2H), 4.23 – 4.15 (m, 2H), 3.94 (s, 2H), 3.50 (S, 1H), 2.89 – 2.82 (m, 1H), 2.31 (s, 1H), 1.31 (d, *J* = 6.8, 6H), 1.24 (t, *J* = 7.2, 3H), 1.22 (d, *J* = 6.8 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 152.4, 149.1, 147.7, 137.1, 123.1, 111.5, 95.5, 80.6, 62.3, 61.8, 60.4, 51.3, 34.3, 28.5, 24.3, 24.1, 23.7, 14.0. HRMS Calcd. for $C_{25}H_{38}N_1O_5S_1$ (M+1): 464. 2471, Found: 464.2472. FTIR (neat): 3353, 2962, 2928, 2870, 1738, 1597, 1567, 1463, 1425, 1385, 1364, 1262, 1193, 1168, 1079, 1052, 1025, 911, 879, 733, 648 cm^{-1}.

Procedure for Desulfinylation and *N*-Protection of the Enyne 3.27

The enyne **3.27** (188 mg, 0.38 mmol, 100 mol%) was dissolved in MeOH (38 mL, 0.01M) and treated with HCl in dioxane (0.5 mL, 4.0 M in dioxane, 500 mol%). The

reaction was allowed to stir at ambient temperature for 1 hour. The reaction mixture was concentrated and coevaporated with MeOH. The residue was dissolved in DCM (38 mL, 0.01M) followed by addition of DIPEA (0.2 mL, 300 mol%) and Boc_2O (125 mg, 0.57 mmol, 150 mol%). The reaction mixture was stirred for 12 hours before diluting with DCM and H_2O. The organic phase was washed with an aqueous solution of citric acid (10 wt%), a saturated aqueous solution of $NaHCO_3$ and with H_2O. After drying (Na_2SO_4), the organic phase was evaporated *in vacuo* and the residue was purified by silica gel column chromatography

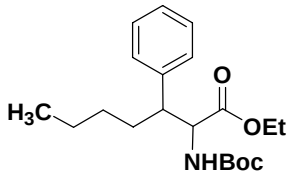


3.33

2-*tert*-Butoxycarbonylamino-3-phenyl-hept-3-en-5-ynoic acid ethyl ester (3.33). Rf = 0.5 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.47 – 7.36 (m, 2H), 7.37 – 7.27 (m, 3H), 5.85 (d, *J* = 2.0 Hz, 1H), 5.36 (d, *J* = 7.2 Hz, 1H), 5.12 (d, *J* = 7.6 Hz, 1H), 4.19 – 4.07 (m, 2H), 1.84 (d, *J* = 2.4, 3H), 1.42 (s, 9H), 1.15 (t, *J* = 6.8, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.4, 154.6, 146.1, 136.9, 128.3, 127.9, 110.9, 91.4, 80.0, 61.7, 58.7, 28.2, 13.9, 4.5. HRMS Calcd. for $C_{20}H_{26}N_1O_4$ (M+1): 344.1862, Found: 344.1861. FTIR (neat): 3375, 2978, 2932, 1740, 1717, 1495, 1367, 1325, 1247, 1164, 1054, 1026, 913, 865, 744, 699 cm^{-1}.

Exhaustive Hydrogenation of Enyne Product of the Enyne 3.33

To a solution of enyne **3.33** (44 mg, 0.13 mmol, 100 mol%) in DCM (1.3 mL, 0.1M) at ambient temperature was added Ir(COD)(Pyr)[P(*c*-Hex)$_3$]PF$_6$ (5.2 mg, 0.03 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 24 hours. The title compound was purified by flash silica chromatography



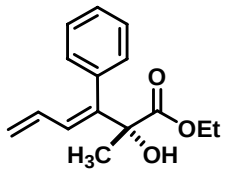
3.34
(mixture of two diastereomers)

2-*tert*-Butoxycarbonylamino-3-phenyl-heptanoic acid ethyl ester (3.34). Rf = 0.6, 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 – 7.11 (m, 5H), 5.04 and 4.78 (major: d, *J* = 9.2 Hz, minor: d, *J* = 8.8 Hz, 1H), 4.57 and 4.45 (minor: dd, *J* = 9.6, 5.2 Hz, major: t, *J* = 8.0 Hz, 1H), 4.12 and 3.97 (minor: q, *J* = 7.2 Hz, major: q, *J* = 7.2 Hz, 2H), 3.18 – 3.15 and 2.91 – 2.86 (minor: m, major: m, 1H), 1.82 – 1.74 (m, 2H), 1.42 and 1.41 (major: s, minor: s, 9H), 1.38 – 1.01 (m, 7H), 0.85 – 0.80 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) Major: 171.7, 155.1, 139.9, 128.4, 128.2, 126.9, 79.7, 60.8, 58.4, 49.3, 30.7, 29.5, 28.2, 22.5, 13.8. Minor: 171.7, 155.6, 139.4, 128.4, 128.2, 127.1, 79.7, 61.0, 57.6, 47.8, 31.1, 29.4, 28.2, 22.5, 14.1. HRMS Calcd. for $C_{20}H_{32}N_1O_4$ (M+1): 350.2331, Found: 350.2329. FTIR (neat): 3359, 2958, 2932, 2870, 1718, 1496, 1454, 1367, 1250, 1171, 1055, 1027, 864, 700 cm^{-1}.

3.6.4 Reductive Coupling of 1,3-Enynes and α-Ketoesters

Representative Procedure for the Coupling of 1,3-Phenyl enyne and Ethyl pyruvate

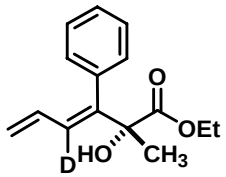
To a solution of $Rh(COD)_2OTf$ (1.9 mg, 0.004 mmol, 2 mol%), (R)-xylyl-WALPHOS (3.2 mg, 0.004 mmol, 2 mol%) and triphenyl acetic acid (0.6 mg, 0.002 mmol, 1 mol%) in DCE (0.5 mL) was added a solution of ethyl pyruvate (24 mg, 0.20 mmol, 100 mol%) and enyne **6a** (50.9 mg, 0.40 mmol, 200 mol%) in DCE (0.5 mL) at 45 ^oC. The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at 45 ^oC under 1 atm of hydrogen for 3 hours. The title compound was purified by flash silical chromatography (Rf = 0.3, 15% EtOAc/hexane) to afford 45.5 mg of the diene **3.35** as a colorless oil (91% yield).



3.35

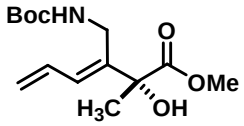
2-Hydroxy-2-methyl-3-phenyl-hexa-3,5-dienoic acid ethyl (3.35). Rf = 0.3, 15% EtOAc /hexane); colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 7.33 – 7.25 (m, 3H), 7.11 – 7.08 (m, 2H), 6.50 (d, *J* = 10.8 Hz, 1H), 5.95 (ddd, *J* = 18.7, 10.3, 10.1 Hz, 1H), 5.24 (ddd, *J* = 18.8, 1.8, 0.6 Hz, 1H), 5.01 (ddd, *J* = 10.2, 2.0, 0.6 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.37 (s, br, 1H), 1.59 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.3, 144.1, 137.6, 133.9, 129.8, 128.7, 127.9, 127.4, 119.2, 76.7, 62.0, 24.1, 13.9. HRMS Calcd. for $C_{15}H_{17}O_3$ [M+1]: 246.1256, Found: 246.1259. FTIR (neat): 3509, 2982, 2938, 2905, 2874, 1955, 1815, 1727, 1635, 1602, 1573, 1492, 1443, 1417, 1373,

1250, 1165, 1128, 1094, 1018, 996, 977, 913, 859, 778, 744, 707, 670, 587 cm^{-1}. HPLC (Chiralcel OJ-H column, 2% i-PrOH/hexane, 0.5 mL/min, 254 nm), t_{minor} = 18.4 min, t_{major} = 24.4; ee = 92%.



***deuterio*-3.35**

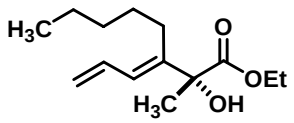
4-*deuterio*-2-Hydroxy-2-methyl-3-phenyl-hexa-3,5-dienoic acid ethyl (*deuterio*-3.35). Rf = 0.3, 15% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.33 - 7.25 (m, 3H), 7.11 - 7.08 (m, 2H), 5.99 (dd, *J* = 17.0, 10.28 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.04 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.39 (s, 1H), 1.59 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.3, 144.0, 137.0, 133.9, 129.8, 128.4 (t, *J* = 24.3 Hz), 127.9, 127.4, 119.2, 76.7, 62.1, 24.1, 14.0. HRMS Calcd. for $C_{15}H_{17}2H_1O_3$ [M]: 247.1319, Found: 247.1317. FTIR (neat): 3501, 2982, 2937, 1727, 1601, 1492, 1443, 1417, 1245, 1165, 1128, 1018, 994, 909, 858, 766, 705 cm^{-1}.



3.37

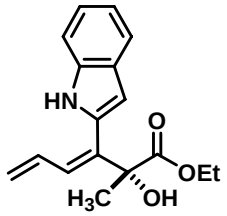
3-(tert-Butoxycarbonylamino-methyl)-2-hydroxy-2-methyl-hexa-3,5-dienoic acid methyl (3.37). Rf = 0.14, 20 %EtOAc/hexane; a white crystal; ^{1}H NMR (400 MHz, $CDCl_3$): 6.71 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.32 (d, *J* = 11.2 Hz, 1H), 5.35 (dd, *J* = 16.8,

1.2 Hz, 1H), 5.30 (dd, *J* = 10.4, 1.2Hz, 1H), 4.80 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.95 (s, 1H), 3.77 (s, 3H), 3.73 (dd, *J* = 13.6, 3.2 Hz, 1H) 1.59 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.5, 155.9, 138.6, 132.1, 130.7, 121.4, 79.7, 76.7, 53.5, 37.4, 28.6, 25.1. HRMS Calcd. for $C_{14}H_{23}NO_5$ (M+1): 286.1654, Found: 286.1654. FTIR(neat): 3449, 3053, 2983, 2253, 1729, 1504, 1456, 1368, 1265, 1165, 976, 912, 741, 651. HPLC (Chiralcel OD column, 1% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{minor} = 19.3 min, t_{major} = 22.5 min; ee = 90%.



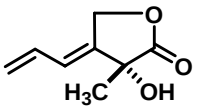
4.38

3-Allylidene-2-hydroxy-2-methyl-octanoic acid ethyl ester (4.38). Rf = 0.3, 10% EtOAc /hexane); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.52 (ddd, *J* = 16.7, 10.5, 10.5 Hz, 1H), 6.20 (d, *J* = 10.8 Hz, 1H), 5.23 (dd, *J* = 16.6, 2.2 Hz, 1H), 5.14 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.26 – 4.13 (m, 2H), 3.38 (d, br, 1H), 2.22 (ddd, *J* = 13.7, 10.3, 6.1 Hz, 1H), 2.08 (ddd, *J* = 13.7, 10.3, 6.1,1H), 1.52 (s, 3H), 1.42 -1.22 (m, 6H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.9, 143.4, 132.8, 126.3, 118.3, 77.0, 62.1, 32.3, 30.4, 27.9, 24.4, 22.4, 14.1, 14.0. HRMS Calcd. for $C_{14}H_{24}O_3$ [M+1]: 241.1804, Found: 241.1802. FTIR (neat): 3508, 3081, 3055, 2980, 2937, 2879, 1724, 1602, 1493, 1463, 1442, 1417, 1367, 1285, 1238, 1162, 1140, 1073, 1025, 996, 913, 860, 777, 707, 670 cm^{-1}. HPLC **(**Chiralpak AD column, 0.1 % i-PrOH/hexane, 0.5 mL/min, 254 nm), t_{minor} = 12.3 min, t_{major} = 13.0; ee = 91%.



3.39

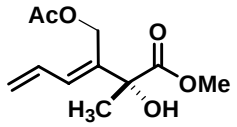
2-Hydroxy-3-(1H-indol-2-yl)-2-methyl-hexa-3,5-dienoic acid ethyl ester (3.39). Rf = 0.25, 15% EtOAc/hexane; colorless oil; H NMR (400 MHz, $CDCl_3$): 8.92 (s, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.67 (td, *J* = 7.5, 0.8 Hz, 1H), 7.08 (td, *J* = 7.0, 0.8 Hz, 1H), 6.72 (dt, *J* = 16.8, 10.3 Hz, 1H), 6.44 (dd, *J* = 5.8, 4.6 Hz, 1H), 6.45 (s, 1H), 5.43 (dt, *J* = 16.8, 0.9 Hz, 1H), 5.23 (dt, *J* = 10.2, 0.9 Hz, 1H), 5.23 (dt, *J* = 10.2, 0.9 Hz, 1H), 4.25 – 4.14 (m, 2H), 3.78 (s, 1H), 1.61 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.4, 135.8, 134.0, 133.8, 133.0, 130.9, 127.7, 122.1, 121.0, 120.3, 119.7, 111.0, 105.4, 77.4, 62.5, 24.4, 14.0. HRMS Calcd. for $C_{17}H_{19}N_1O_3$ [M+1]: 286.1443, Found: 286.1439. FTIR (neat): 3407, 3055, 2981, 2936, 1727, 1617, 1454, 1398, 1371, 1318, 1255, 1129, 1017, 916, 858, 796, 738, 702 cm^{-1}. HPLC **(**Chiralcel OJ-H column, 5% i-PrOH/hexane, 0.4 mL/min, 254 nm), t_{minor} = 41.7 min, t_{major} = 46.5; ee = 93%.



3.40

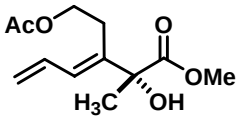
4-Allylidene-3-hydroxy-3-methyl-dihydro-furan-2-one (3.40). Rf = 0.1, 20 % EtOAc/ hexane; colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 6.34 (dt, *J* = 11.2, 2.0 Hz, 1H), 6.29 (m, 1H), 5.39 (d, *J* = 14.4 Hz, 1H), 5.32 (d, *J* = 9.2 Hz, 1H), 5.09 (dd, *J* = 14.0, 2.4 Hz,

1H), 4.93 (dd, *J* = 14.0, 2.4 Hz, 1H), 3.21 (s, 1H), 1.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.4, 137.0, 130.3, 124.8, 121.3, 71.7, 67.7, 25.9. HRMS Calcd. for $C_8H_{10}O_3$ (M+1): 154.0630, Found: 154.0632. FTIR (neat): 3438, 2982, 2890, 2254, 1778, 1609, 1466, 1440, 1374, 1361, 1265, 1203, 1165, 1117, 1017, 1001, 909, 732, 650, 588. HPLC (Chiralcel OJH column, 0.5% [0 – 30 min] – 3% [30 – 120 min] *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{major} = 86.8 min, t_{minor} = 90.8 min; ee = 91%.



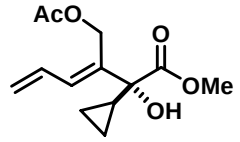
3.41

3-Acetoxymethyl-2-hydroxy-2-methyl-hexa-3,5-dienoic acid methyl ester (3.41). Rf = 0.1, 20 % EtOAc/hexane; a colorless oil; ^{1}H NMR(400 MHz, $CDCl_3$): 6.67 (dt, *J* = 16.8, 11.2 Hz, 1H), 6.47 (d, *J* = 11.2 Hz, 1H), 5.42 (dd, *J* = 16.4, 1.2 Hz, 1H), 5.34 (dd, *J* = 10.0, 1.2 Hz, 1H), 4.84 (d, *J* = 12 Hz, 1H), 4.83 (d, *J* = 12 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 1H), 2.02 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.8, 170.6, 135.8, 132.3, 131.4, 121.9, 75.5, 58.8, 53.0, 24.7, 20.7. HRMS Calcd. for $C_{11}H_{16}O_5$ (M + 1): 229.1076, Found: 229.1083. FTIR (neat): 3517, 3054, 2986, 2253, 1734, 1421, 1373, 1265, 1132, 1024, 988, 911, 741, 651. HPLC (Chiralcel OD column, 1% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{minor} = 18.3 min, t_{major} = 21.1 min; ee = 90%.



3.42

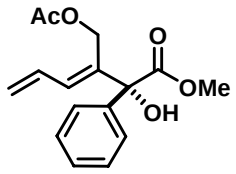
3-(2-Acetoxy-ethyl)-2-hydroxy-2-methyl-hexa-3,5-dienoic acid methyl ester (3.42). Rf = 0.15, 20 % EtOAc/hexane; colorless oil; ^{1}H NMR(400 MHz, $CDCl_3$): 6.62 (dt, *J* = 16.8, 10.4 Hz, 1H), 6.31 (d, *J* = 10.8 Hz, 1H), 5.33 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.10 (m, 2H), 3.79 (s, 3H), 3.58 (s, 1H), 2.66 (m, 1H), 2.44 (m, 1H), 2.04 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.0, 171.0, 137.4, 132.3, 129.4, 120.0, 63.7, 53.1, 27.1, 24.6, 20.9. HRMS Calcd. for $C_{12}H_{18}O_5$ (M+1): 243.1232, Found: 243.1236. FTIR (neat):3438, 3053, 2986, 2253, 1732, 1645, 1437, 1421, 1365, 1265, 1131, 1095, 1034, 990, 911, 732, 651. HPLC (Chiralcel OD column, 1% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{minor} = 16.5 min, t_{major} = 19.7 min; ee = 92%.



3.43

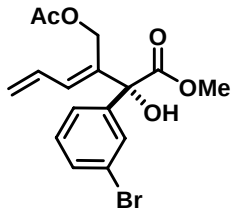
3-Acetoxymethyl-2-cyclopropyl-2-hydroxy-hexa-3,5-dienoic acid methyl ester (3.43). Rf = 0.4, 20% EtOAc/hexane; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.72 – 6.62 (m, 2H), 5.44 – 5.37 (m, 1H), 5.33 – 5.29 (m, 1H), 4.81 (q, *J* = 13.9 Hz, 4H), 3.78 (s, 3H), 3.34 (s, 1H), 1.99 (s, 3H), 1.41 – 1.35 (m, 1H), 0.54 – 0.43 (m, 3H), 0.39 – 0.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.2, 170.6, 135.4, 133.3, 131.6, 121.9, 75.4, 59.3, 53.2, 20.8, 15.9, 1.07, 0.04. HRMS Calcd. for $C_{13}H_{18}N_1O_5$ [M]: 254.1154, Found:.254.1155. FTIR (neat): 3490, 3088, 3010, 2954, 1736, 1598, 1436, 1380, 1364,

1233, 1162, 1026, 990, 960, 921, 833, 792 cm^{-1}. HPLC **(**Chiralpak AD-H column, 1% i-PrOH/hexane, 1.0 mL/min, 254 nm), t_{minor} = 21.0 min, t_{major} = 26.8; ee = 88%.



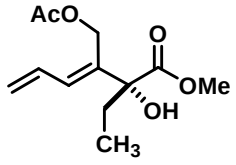
3.44

3-Acetoxymethyl-2-hydroxy-2-phenyl-hexa-3,5-dienoic acid methyl ester (3.44). Rf = 0.21, 20 %EtOAc/hexane; colorless oil; ^{1}H NMR(400 MHz, $CDCl_3$): 7.49 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.34 (m, 3H), 6.65 (dt, *J* = 16.0, 10 Hz, 1H), 6.15 (d, *J* = 10.8 Hz, 1H), 5.30 (dd, *J* = 5.2, 1.2 Hz, 1H), 5.28 (dd, *J* = 12.4, 1.2 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.15 (s, 1H), 3.84 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.0, 170.7, 139.4, 135.8, 134.4, 131.4, 128.1, 126.9, 122.2, 81.4, 59.8, 53.3, 20.6. HRMS Calcd. for $C_{16}H_{18}O_5$ [M+1]: 291.1232, Found: 291.1235. FTIR (neat): 3500, 3053, 2986, 2253, 1732, 1651, 1436, 1422, 1383, 1265, 1130, 1093, 1063, 1025, 989, 912, 741, 651. HPLC (Chiralpak ADH column, 1% [0 min] – 5% [90 min] *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{minor} = 38.5 min, t_{major} = 43.0 min; ee = 91%.



3.45

3-Acetoxymethyl-2-(2-bromo-phenyl)-2-hydroxy-hexa-3,5-dienoic acid methyl ester (3.45). Rf = 0.14, 20 %EtOAc/hexane; colorless oil; ^{1}H NMR(400 MHz, $CDCl_3$): 7.70 (d, *J* = 2.0 Hz, 1H), 7.50 (dt, *J* = 6.0, 1.2 Hz 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 6.64 (dt, *J* = 17.2, 10.0 Hz, 1H), 6.12 (d, *J* = 11.2 Hz, 1H), 5.35 (dd, *J* = 3.2, 1.6 Hz, 1H), 5.32 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.80 (d, *J* = 12.8 Hz, 1H), 4.76 (d, *J* = 12.8 Hz, 1H), 4.19 (s, 1H), 3.86 (s, 3H), 1.98 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 170.8, 141.6, 135.4, 134.6, 131.3, 130.2, 129.6, 125.8, 122.8, 122.4, 81.0, 59.7, 53.6, 20.7. HRMS Calcd. for $C_{16}H_{17}O_5Br$ [M+1]: 369.0338, Found: 369.0340. FTIR (neat): 3500, 3053, 2986, 2253, 1733, 1594, 1568, 1472, 1427, 1421, 1383, 1265, 1179, 1133, 1075, 1025, 988, 911, 748, 651. HPLC (Chiralpak ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm), t_{minor} = 8.8 min, t_{major} = 10.5 min; ee = 90%.



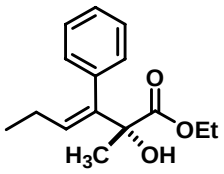
3.46

3-Acetoxymethyl-2-ethyl-2-hydroxy-hexa-3,5-dienoic acid methyl ester (3.46). Rf = 0.3, 20% EtOAc/hexane; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.64 (ddd, *J* = 16.6, 11.0, 10.2 Hz, 1H), 6.62 (d, *J* = 11.2 Hz, 1H), 5.37 (dd, *J* = 16.4, 1.6 Hz, 1H), 5.29 (dd, *J* = 10.0, 1.6 Hz, 1H), 4.80 (s, 2H), 3.75 (s, 3H), 3.58 (s, br, 1H), 1.99 (dt, J = 21.2, 7.4,

1H), 1.99 (s, 3H), 1.81 (dt, J = 21.2, 7.4 Hz, 1H), 0.86 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.4, 170.7, 135.2, 133.0, 131.6, 121.8, 78.5, 58.9, 53.1, 30.0, 20.8, 7.7. HRMS Calcd. for $C_{12}H_{18}O_5$ [M]: 242.1154, Found: 242.1156. FTIR (neat): 3502, 3087, 2956, 2881, 1736, 1597, 1437, 1382, 1364, 1320, 1236, 1149, 1065, 1023, 990, 960, 925, 808, 756 cm^{-1}. HPLC **(**Chiralpak AD-H column, 1% i-PrOH/hexane, 1.0 mL/min, 254 nm), t_{minor} = 20.0 min, t_{major} = 30.1; ee = 86 %.

Procedure for Site-Selective Hydrogenation of the Diene 3.35

To a solution of diene **3.35.** (100 mg, 0.406 mmol, 100 mol%) in toluene (2.7 mL, 0.15M) was added $RhCl(PPh_3)_3$ (38 mg, 0.0406 mmol, 10 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 4 hours. The title compound was purified by flash silica chromatography (Rf = 0.3, 15% EtOAc/hexane) to afford 97.8 mg as a colorless oil (97% yield).



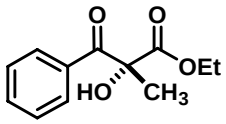
3.47

2-Hydroxy-2-methyl-3-phenyl-hex-3-enoic acid ethyl ester (3.47). ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 – 7.22 (m, 3H), 7.07 – 7.04 (m, 2H), 5.89 (t, J = 7.4 Hz, 1H), 4.17 – 4.04 (m, 2H), 3.26 (s, br, 1H), 1.77 (qt, J = 7.4, 2H), 1.55 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.7, 141.7, 137.6, 131.0, 129.6, 127.8, 127.0, 76.7, 61.8, 24.0, 22.3, 14.0. HRMS Calcd. for $C_{15}H_{20}O_3$ [M]: 248.1412, Found: 248.1415.

FTIR (neat): 3507, 3054, 2964, 2935, 2872, 1726, 1599, 1573, 1492, 1442, 1373, 1300, 1248, 1159, 1137, 1122, 1093, 1020, 969, 859, 764, 704, 678 cm^{-1}.

Procedure for Ozonolysis of Compound 3.47.

Compound **3.47** (46.6 mg, 0.186 mmol, 100 mol%) was dissolved in DCM (9.3 mL, 0.02M), and the solution was cooled to -78 °C. The solution was sparged with ozone for 5 min, and sparged with argon for 5 min. Triphenylphosphine (245 mg, 0.934 mmol, 500 mol%) was added, and the reaction was allowed to stir for 10 hours while warming gradually to room temperature. The solvent was removed *in vacuo*. The title compound was purified by flash silical chromatography (Rf = 0.25, 15% EtOAc/hexane) to afford 38.6 mg as a colorless oil (93% yield).

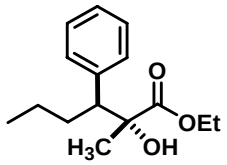


6d

2-Hydroxy-2-methyl-3-oxo-3-phenyl-propionic acid ethyl ester (6d). ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 – 7.94 (m, 2H), 7.56 (tt, *J* = 7.4, 1.5 Hz, 1H), 7.46 – 7.41 (m, 2H), 4.43 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.72 (s, 3H), 1.14 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 195.9, 172.3, 133.7, 133.1, 129.4, 128.6, 79.4, 62.5, 23.5, 13.8. HRMS Calcd. for $C_{12}H_{14}O_4$ [M+1]: 223.0970, Found: 223.0973. FTIR (neat): 3472, 2975, 2940, 2848, 1732, 1679, 1618, 1443, 1391, 1374, 1251, 1159,1122, 1017, 972, 858, 784, 750, 707 cm^{-1}.

Procedure for the Exhaustive Hydrogenation of the Diene 3.35.

To a solution of diene product **3.35** (103mg, 0.418 mmol, 100 mol%) in DCM (5 mL, 0.1M) at ambient temperature was added Ir(COD)(Pyr)[P(*c*-Hex)$_3$]PF$_6$ (17mg, 0.0209 mmol, 5 mol%). The system was purged with argon gas followed by hydrogen gas. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 3 hours. The title compound was purified by flash silical chromatography (Rf = 0.3, 15% EtOAc/hexane) to afford 97.3 mg as a colorless oil (93% yield, 12:1 d.r.).

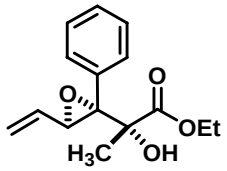


3.49
(mixture of two diastereomers)

2-Hydroxy-2-methyl-3-phenyl-hexanoic acid ethyl (3.49). ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 - 7.29 (m, 3H), 7.28 - 7.22 (m, 2H), 4.34 – 4.21 and 4.05 -3.89 (major: m, 2H, minor: m, 2H), 3.13 (s, 1H), 2.89 and 2.88 (major: dd, *J* = 11.6, 3.2 Hz, 1H), minor: dd, *J* = 11.6, 4.4 Hz, 1H), 1.95 – 1.81 (m, 1H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.17 – 0.35 (m, 4H), 1.14 (s, 3H), 0.85 and 0.80 (minor: t, *J* = 7.4 Hz, 3H, major: t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): Major: 177.5, 139.7, 129.8, 127.9, 126.7, 62.0, 52.7, 32.6, 25.0, 20.5, 14.2, 13.8. Minor:176.5, 140.3, 128.9, 127.9, 126.8, 61.6, 52.7, 30.2, 24.4, 20.6, 14.0, 13.9. HRMS Calcd. for $C_{15}H_{22}O_3$ [M+1]: 251.1647, Found: 251.1651. FTIR (neat): 3517, 3028, 2957, 2934, 2871, 1725, 1602, 1492, 1453, 1373, 1241, 1161, 1108, 1019, 949, 912, 866, 771, 707 cm^{-1}.

Procedure for Epoxidation of the Diene 3.35

To a solution of $VO(acac)_2$ (1.1 mg, 0.0041 mmol, 2.5 mol%) and compound **3.35** (40.5 mg, 0.16 mmol, 100 mol%) in DCM (1.6 mL, 0.1 M) was added *t*-BuOOH (5 – 6 M in Decane, 0.04 mL, 0.20 mmol, 125 mol%). The reaction mixture was allowed to stir at room temperature for 4 hours under argon atmosphere. After removing of the solvent by evaporation, the title compound was purified by flash column chromatography (Rf = 0.31, 20 %EtOAc/hexane) to afford 40.4 mg as a colorless oil (94 % yield, 7:1 d.r.).

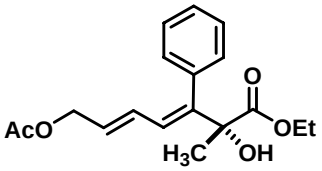


3.50
(mixture of two diastereomers)

2-Hydroxy-2-(2-phenyl-3-vinyl-oxiranyl)-propionic acid ethyl ester (3.50). ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 – 7.24 (m, 5H), 5.50 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.24 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.06 – 4.99 (m, 1H), 4.14 – 4.02 (m, 2H), 3.88 (d, *J* = 8.8 Hz, 1H), 3.49 and 3.36 (minor: s, 1H, major: s, 1H), 1.54 and 1.41 (major: s, 3H, minor: s, 3H), 1.18 and 1.13 (minor: t, *J* = 7.2 Hz, 3H, major: t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): Major: 173.2, 133.9, 133.2, 128.5, 128.2, 127.8, 121.5, 75.7, 69.6, 61.7, 59.7, 20.7, 13.8. Minor: 134.5, 68.0, 62.2, 40.0, 20.9. HRMS Calcd. for $C_{15}H_{18}O_4$ [M+1]: 263.1283, Found: 263.1280. FTIR (neat): 3445, 2983, 2253, 1733, 1710, 1509, 1455, 1393, 1368, 1265, 1165, 1069, 981, 912, 732, 650.

Procedure for Cross-Metathesis of the Diene 3.35

To a solution of Grubbs' catalyst (6.2 mg, 0.0073 mmol, 5 mol%) in DCM (0.7 mL, 0.2 M) were added compound **3.35** (36.1 mg, 0.147 mmol, 100 mol%) and 1,4-diacetoxy-cis-2-butene (77.2 mg, 0.45 mmol, 300 mol%). The reaction mixture was allowed to stir at 40 ^{o}C under argon atmosphere for 14 hours. The title compound was purified by flash column chromatography (Rf = 0.18, 20 %EtOAc/hexane) to afford 33.6 mg as a colorless oil (72 % yield, *E:Z* = 5:1).

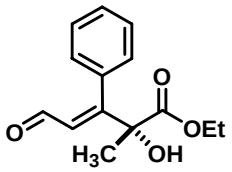


3.54
(mixture of two diastereomers)

7-Acetoxy-2-hydroxy-2-methyl-3-phenyl-hepta-3,5-dienoic acid ethyl ester (3.54). ^{1}H NMR(400 MHz, $CDCl_3$): 7.38 – 7.29 (m, 3H), 7.13 – 7.08 (m, 2H), 6.82 and 6.52 (minor: d, *J* = 10.8 Hz, 1H, major: d, *J* = 10.0 Hz, 1H), 6.00 -5.81 (m, 2H), 5.48 (minor: dt, *J* = 10.8, 7.2 Hz, 1H), 4.80 (minor: d, *J* = 7.2 Hz, 1H), 4.47 (d, *J* = 5.2 Hz, 2H), 4.20 – 4.03 (m, 2H), 3.46 and 3.42 (minor: s, 1H, major: s, 1H), 2.08 and 2.00 (minor: s, 3H, major: s, 3H), 1.62 and 1.60 (minor: s, 3H, major: s, 3H), 1.19 and 1.15 (major: t, *J* = 7.2 Hz, 3H, minor: t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): Major: 175.2, 170.6, 145.2, 136.7, 131.0, 129.7, 128.6, 127.9, 127.6, 126.9, 64.6, 62.1, 24.1, 20.8, 13.9. Minor: 144.5, 137.0, 131.8, 129.8, 128.1. HRMS Calcd. for $C_{18}H_{22}O_5$ [M+1]: 319.1545, Found: 319.1544. FTIR (neat): 3521, 3154, 2984, 2253, 1791, 1726, 1651, 1557, 1471, 1376, 1249, 1165, 1130, 1094, 1021, 976, 912, 732, 651.

Procedure for Oxidative Cleavage of the Diene 3.35.

To a mixture of 0.8 mL of water and 1.9 mL of THF, OsO_4 (5.0 mg, 0.0197 mmol, 5 mol%) and compound **3.35** (97.2 mg, 0.395 mmol, 100 mol%) was added and then stirred for 5 minutes. While the temperature of the stirred mixture was maintained at 24 – 26 °C, $NaIO_4$ (186 mg, 0.868 mmol, 220 mol%) was added in portions over a period of 40 minutes. The solution was stirred for an additional 2 hours. The mixture was extracted thoroughly with ether and the combined organic layers were dried with Na_2SO_4. The solvent was removed *in vacuo*, and then the title compound was purified by flash silical chromatography (Rf = 0.25, 20% EtOAc/hexane) to afford 81.4 mg as a colorless oil (84% yield).



3.53

2-Hydroxy-2-methyl-5-oxo-3-phenyl-pent-3-enoic acid ethyl ester (3.53). ^{1}H NMR (300 MHz, $CDCl_3$): 9.26 (d, *J* = 7.5 Hz, 1H), 7.38 - 7.31 (m, 3H), 7.20 – 7.16 (m, 2H), 6.41 (d, *J* = 8.1 Hz, 1H), 4.22 – 4.05 (m, 2H), 3.59 (s, 1H), 1.62 (s, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 193.7, 173.8, 163.9, 133.8, 129.3, 128.9, 128.6, 128.0, 76.9, 62.7, 23.8, 13.9. HRMS Calcd. for $C_{14}H_{16}O_4$ [M]: 248.1049, Found: 248.1061. FTIR (neat): 3472, 3024, 2975, 2940, 2848, 1732, 1679, 1618, 1443, 1391, 1374, 1251, 1159, 1122, 1017, 972, 858, 784, 750, 707 cm^{-1}.

Determination of Absolute and Relative Stereochemistry

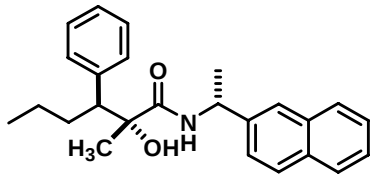
The exhaustive hydrogenation product **3.49** and epoxidation produet **3.50** were converted to amide compound **3.51** and **3.52,** respectively. Then the abosoute and relative stereochemistry of two compounds **3.51** and **3.52** were determined by X-ray analysis.

Synthesis of 3.51

To a solution of **3.49** (121.6 mg, 0.468 mmol) in THF:MeOH:H_2O (3:1:1, 0.8 mL), $LiOH{\cdot}H_2O$ (61.2 mg, 1.485 mmol) was added. The reaction mixture was stirred at 30 ^oC for 12 h. After removal of THF and MeOH using N_2 gas flow, the residue was acidified with 2N HCl (5 mL) and extracted with ethyl acetate (5 x 5 mL). The combined extracts were dried over $MgSO_4$. After filteration and evaporation of the solvent *in vacuo*, 108.4 mg of the acid compound was obtained.

To the stirred solution of the crude acid compound (108.4 mg, 0.486 mmol) in CH_2Cl_2 (5 mL, 0.1M), 1-ethyl-3-(3-dimethylaminopropyl)-carbondiimide hydrochloride (EDCI, 93.2 mg, 0.486 mmol), 1-hydroxybenzotriazole hydrate (65.7 mg, 0.486 mmol), and triethylamine (0.23 mL, 0.535 mmol) at 0 ^oC. The solution was stirred for 10 min. at ^oC. (*R*)-naphthylethylamine (91.5 mg, 0.535 mmol) was added to the reaction mixture a 0 ^oC, and the mixture was stirred for 12 h at room temperature. The solution was washed with 10% aqueous solution of citric acid, saturated aqueous $NaHCO_3$ solution, and the organic layer was dried over $MgSO_4$. After filteration, the dried solution was concentrated under reduced pressure, and the major diastereomer was isolated by flash

column chromatography (Rf = 0.3, 20 % EtOAc/hexane) to afford 102.7 mg as a white solid (56 % yield).



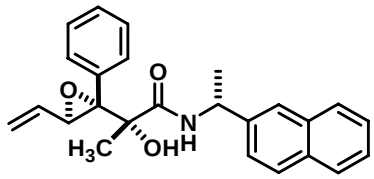
3.51

(*2R,3S,1'R*)-2-Hydroxy-2-methyl-3-phenyl-hexanoic acid (1'-naphthalen-2'-yl-ethyl)-amide (3.51). ^{1}H NMR (400 MHz, $CDCl_3$): 7.82 – 7.75 (m, 4H), 7.48 – 7.41 (m, 3H), 7.33 – 7.22 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 1H), 5.31 (qt, *J* = 7.2 Hz, 1H), 3.08 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.04 (s, br, 1H), 1.95 – 1.85 (m, 1H), 1.61 (d, *J* = 6.8 Hz, 3H), 1.57 – 1.49 (m, 1H), 1.11 (s, 3H), 1.08 – 1.01 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.4, 140.5, 139.8, 133.3, 132.7, 129.6, 128.4, 128.2, 127.8, 127.6, 126.8, 126.2, 125.8, 124.6, 124.5, 77.9, 52.6, 48.5, 31.7, 26.4, 21.7, 20.8, 14.0. HRMS Calcd. for $C_{15}H_{17}O_3$ [M+1]: 246.1256, Found: 246.1259. FTIR (neat): 3394, 3057, 2969, 2934, 2870, 1650, 1601, 1511, 1451, 1376, 1273, 1127, 945, 904, 859, 818, 775, 730 cm^{-1}. MP 158 – 159 ^{o}C.

Synthesis of 3.52

To a solution of **3.50** (121.6 mg, 0.468 mmol) in THF:MeOH:H2O (3:1:1, 0.8 mL), LiOH·H2O (61.2 mg, 1.485 mmol) was added. The reaction mixture was stirred at 30 ^{o}C for 12 h. After removal of THF and MeOH using N_2 gas flow, the residue was acidified with 2 N HCl (5 mL) and extracted with ethyl acetate (5x 5 mL). The combined extracts were dried over $MgSO_4$. After filtration and evaporation of the solvent *in vacuo,* 108.4 mg of acid compound was obtained.

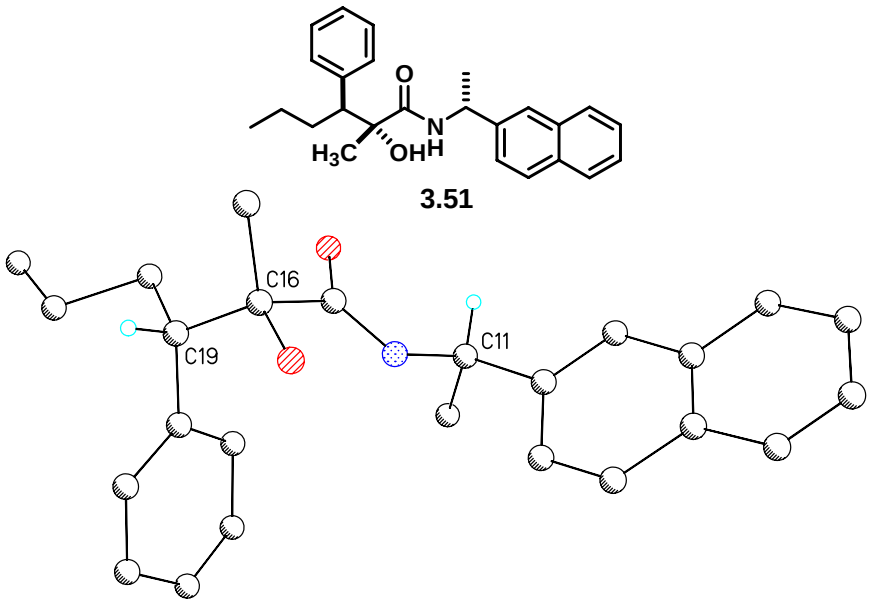
To the stirred solution of the crude acid compound (70.3 mg, 0.30 mmol) in CH_2Cl_2 (3 mL, 0.1M), 1-ethyl-3-(3-dimethylaminopropyl)-carbondiimide hydrochloride (EDCI, 59.0 mg, 0.30 mmol), 1-hydroxybenzotriazole hydrate (40.5 mg, 0.30 mmol), and triethylamine (0.05 mL, 0.33 mmol) at 0 ^oC. The solution was stirred for 10 min. at ^oC. (*R*)-naphthylethylamine (57.0 mg, 0.33 mmol) was added to the reaction mixture a 0 ^oC, and the mixture was stirred for 12 h at room temperature. The solution was washed with 10% aqueous solution of citric acid, saturated aqueous $NaHCO_3$ solution, and the organic layer was dried over $MgSO_4$. After filtration, the dried solution was concentrated under reduced pressure, and the major diastereomer was isolated by flash column chromatography (Rf = 0.2, 20 % EtOAc/hexane) to afford 77.2 mg as a white solid (66 % yield).



3.52

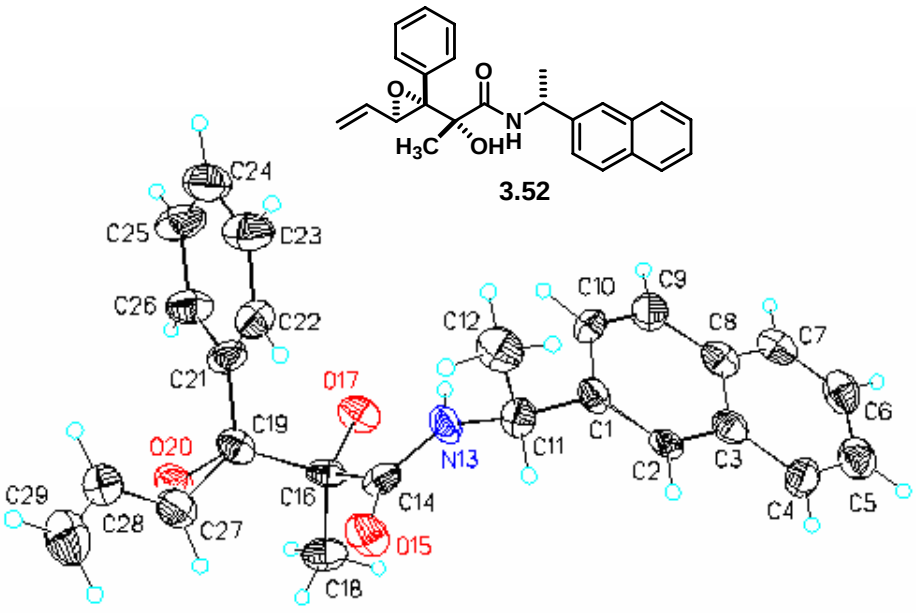
(*2R,1'R*)-(2-Hydroxy-N-(1'-naphthalen-2-yl-ethyl)-2-(2-phenyl-3-vinyl-oxiranyl)-propionamide (3.52). ^1H NMR (400 MHz, $CDCl_3$): 7.81 – 7.78 (m, 3H), 7.73 (s, 1H), 7.48 – 7.42 (m, 2H), 7.40 – 7.37 (m, 3H), 7.32 – 7.29 (m, 3H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.23 – 5.19 (m, 2H), 5.10 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.96 – 4.87 (m, 1H), 3.52 (d, *J* = 8.0 Hz, 1H), 3.47 (d, *J* = 1.6 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): HRMS Calcd. for $C_{25}H_{25}NO_3$ [M]: 387.1834, Found: 387.1843. FTIR (neat): 3379, 3086, 3056, 2976, 2931, 1651, 1601, 1524, 1445, 1365, 1226, 1174, 1113, 985, 929, 819, 749, 712 cm^{-1}. MP 136.5 – 137.5 ^oC.

X-Ray Cystallographic Data for 3.51



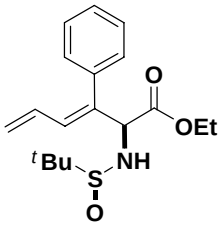
3.51

X-Ray Cystallographic Data for 3.52

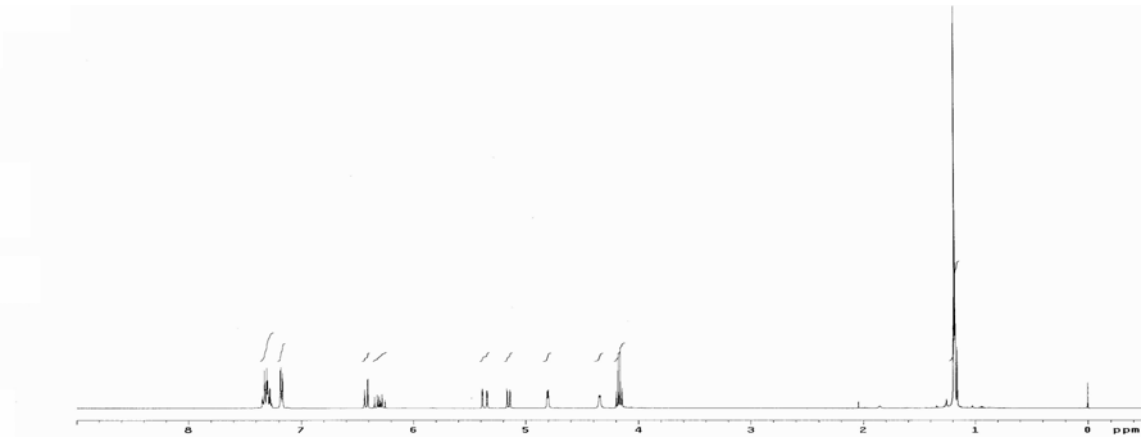


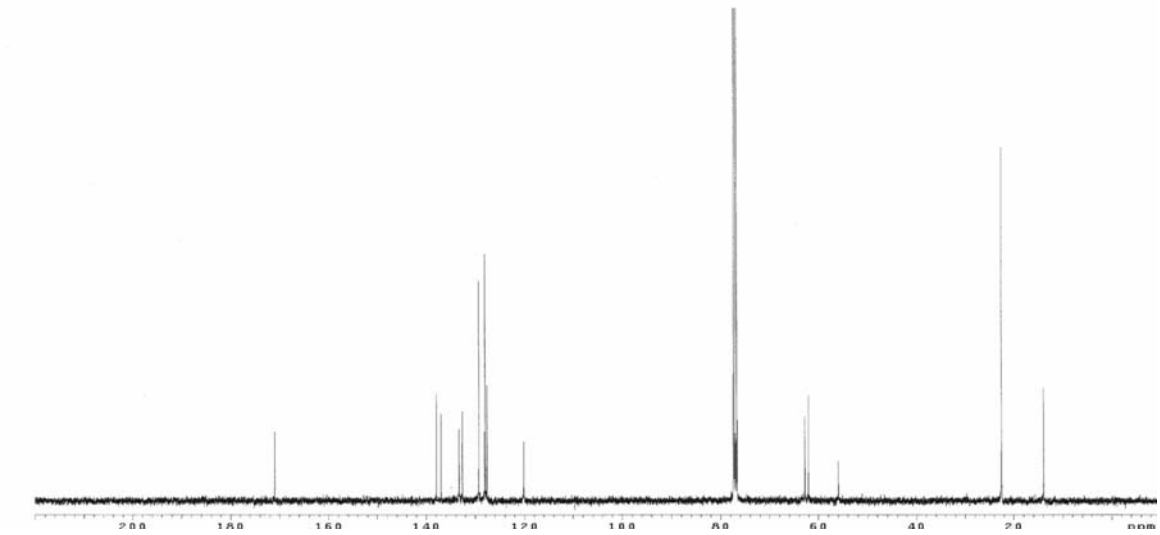
3.52

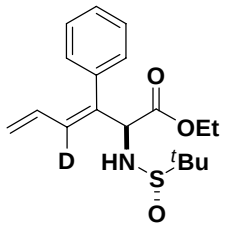
3.7 SPECTRA



3.3






O
OEt
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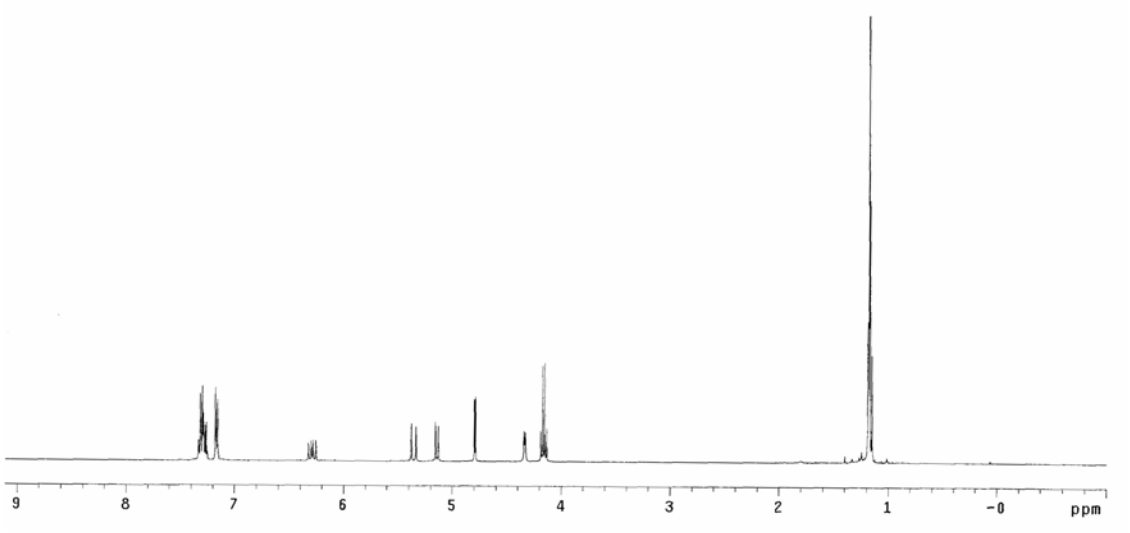
***deuterio*-3.3**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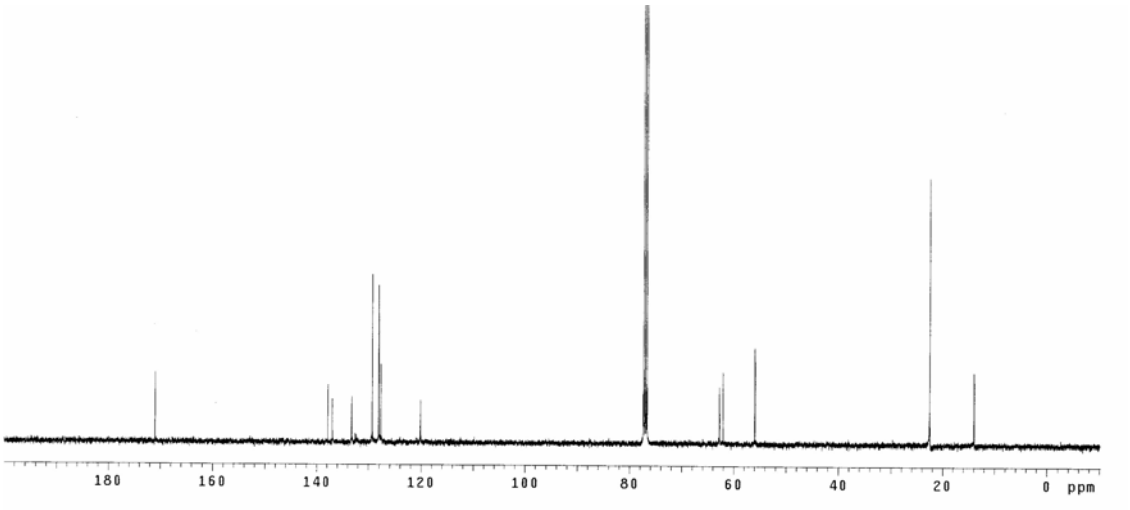
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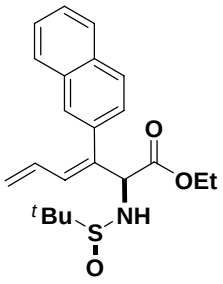
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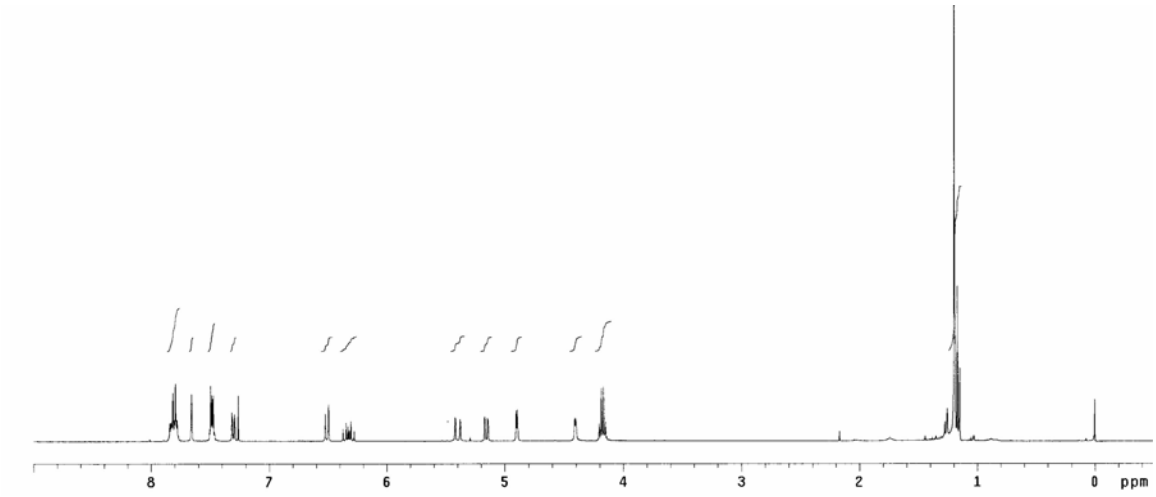
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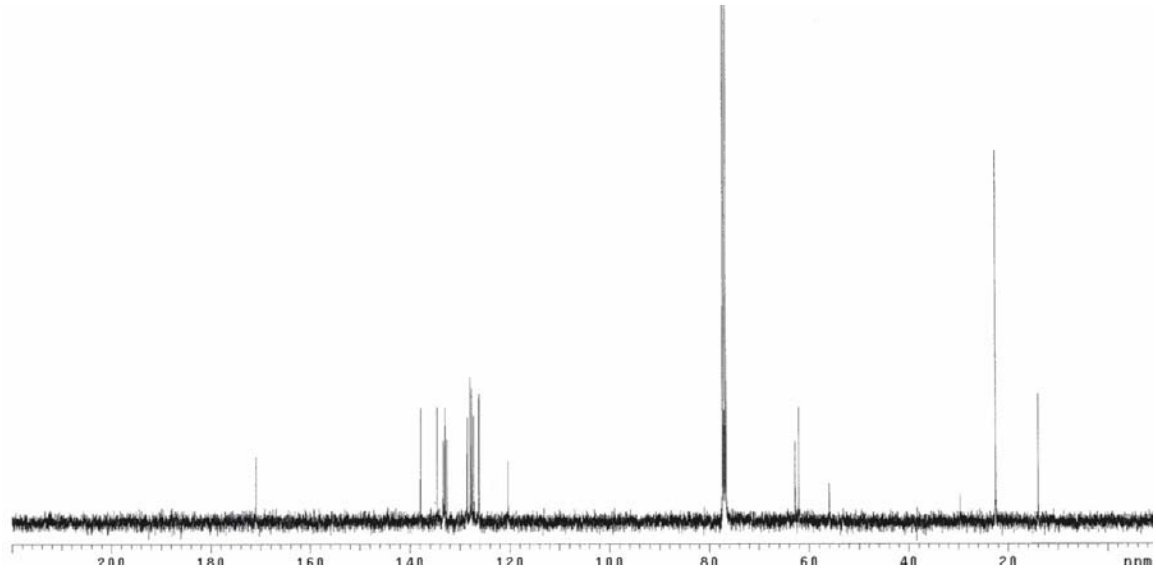
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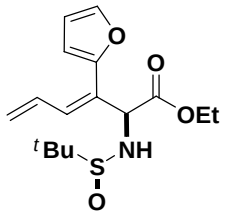
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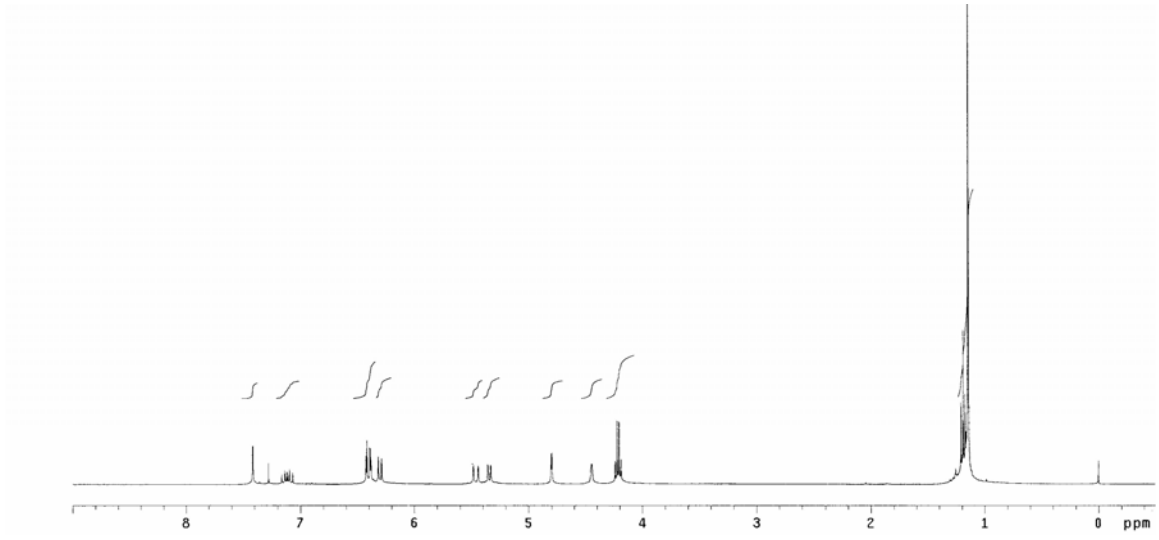
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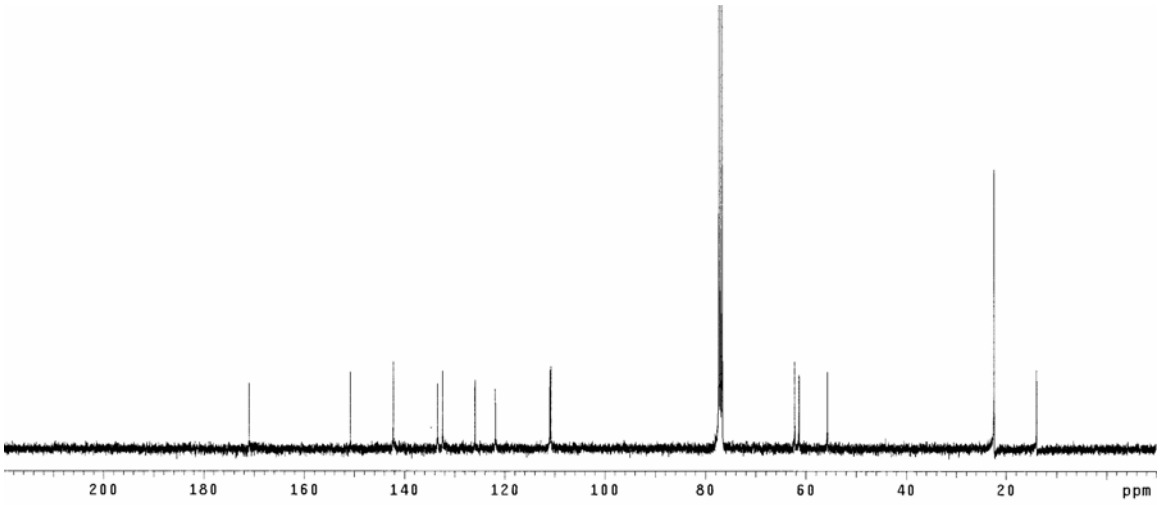
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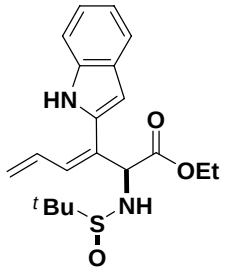
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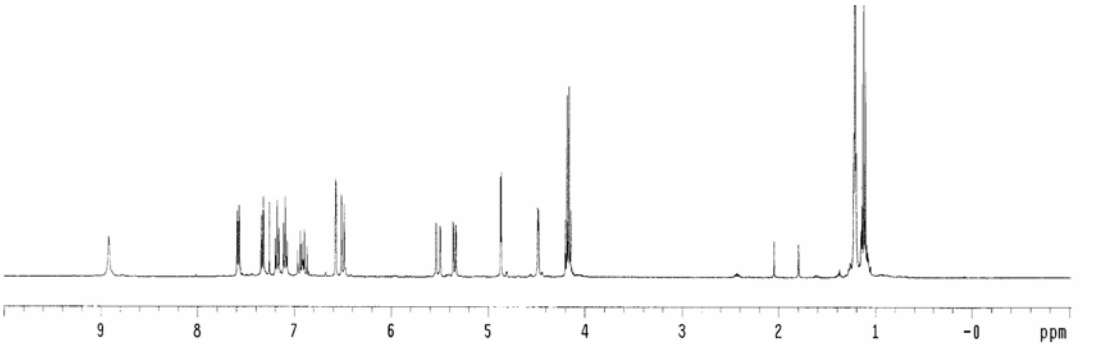
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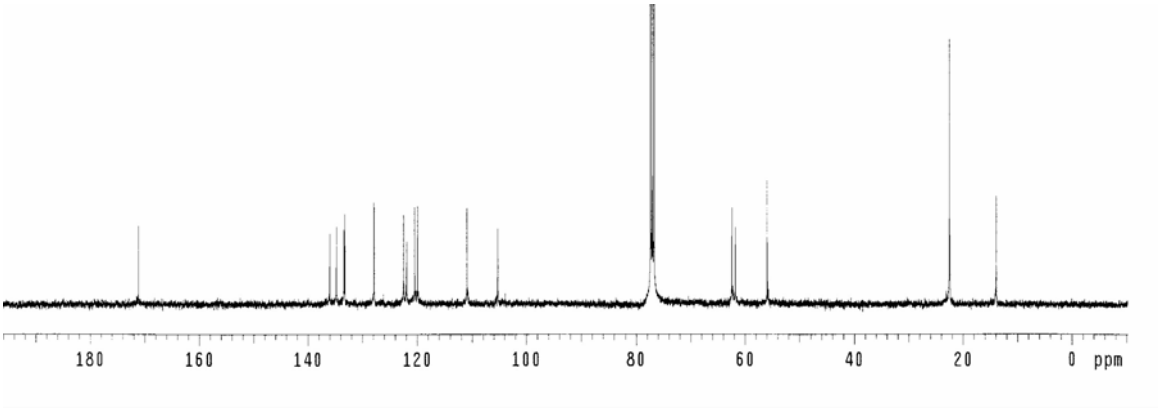
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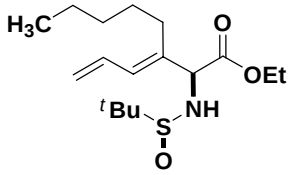
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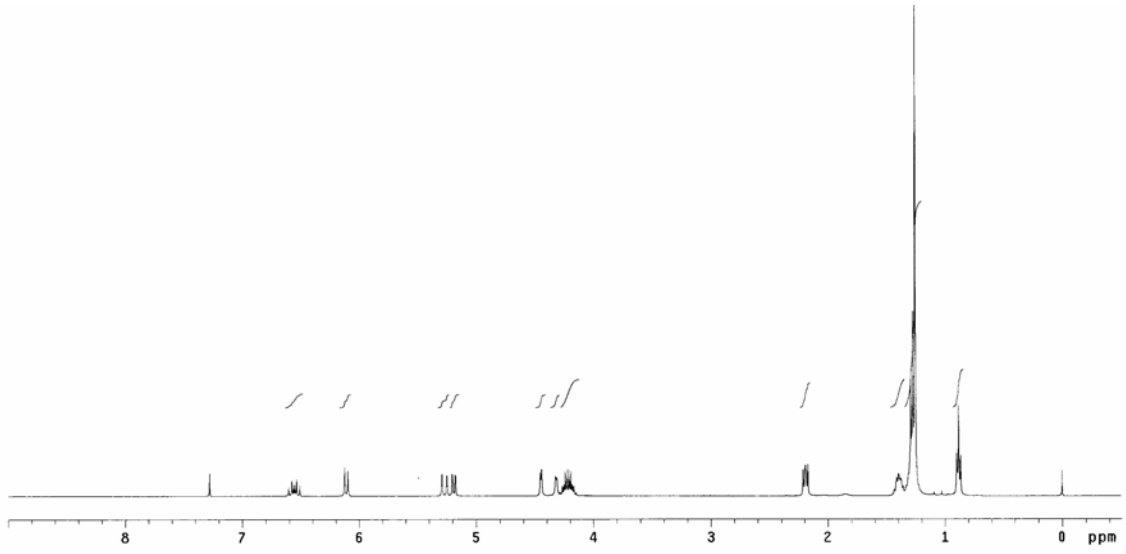
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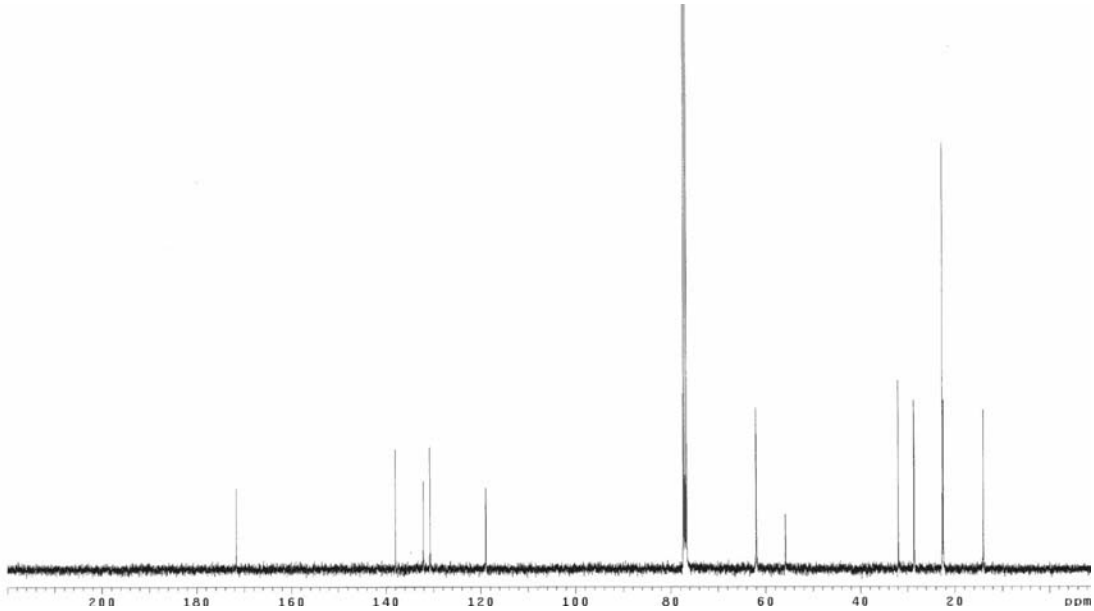
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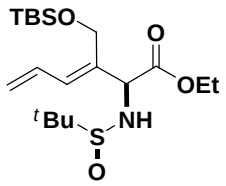
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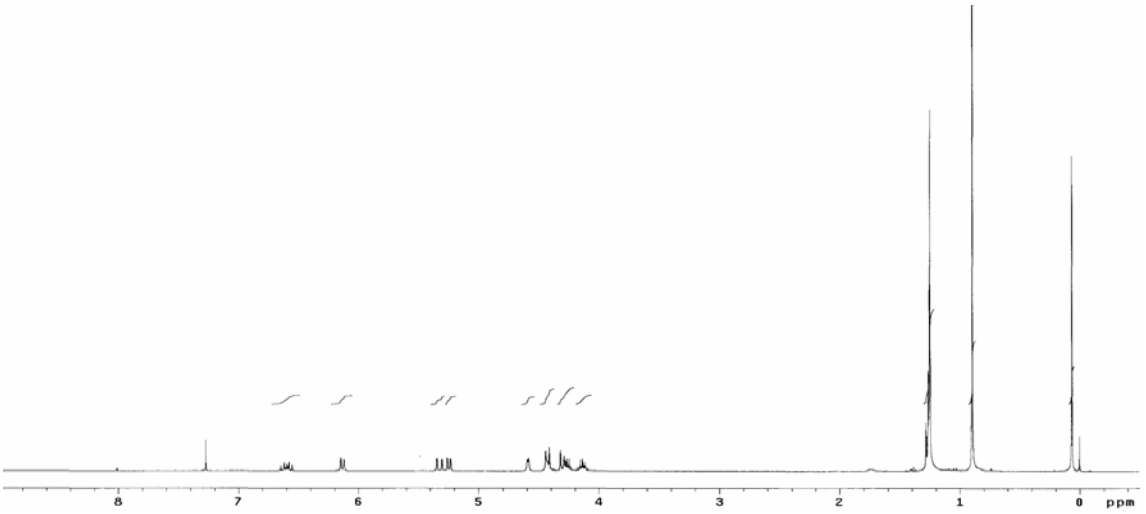
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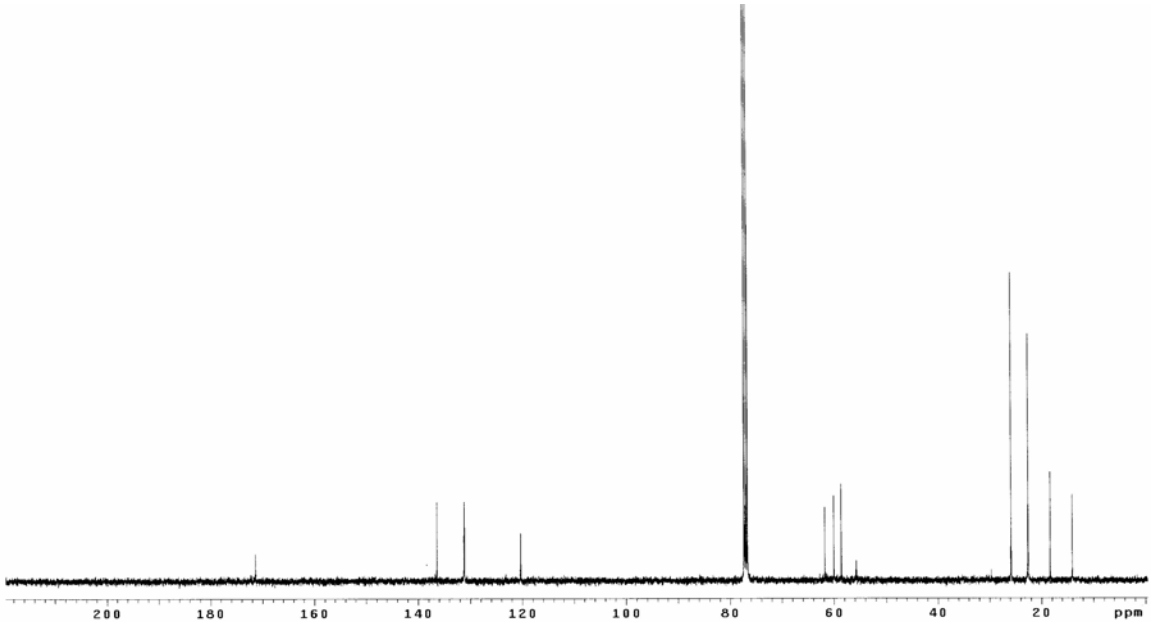
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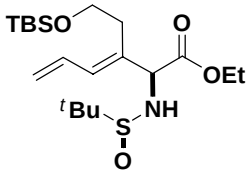
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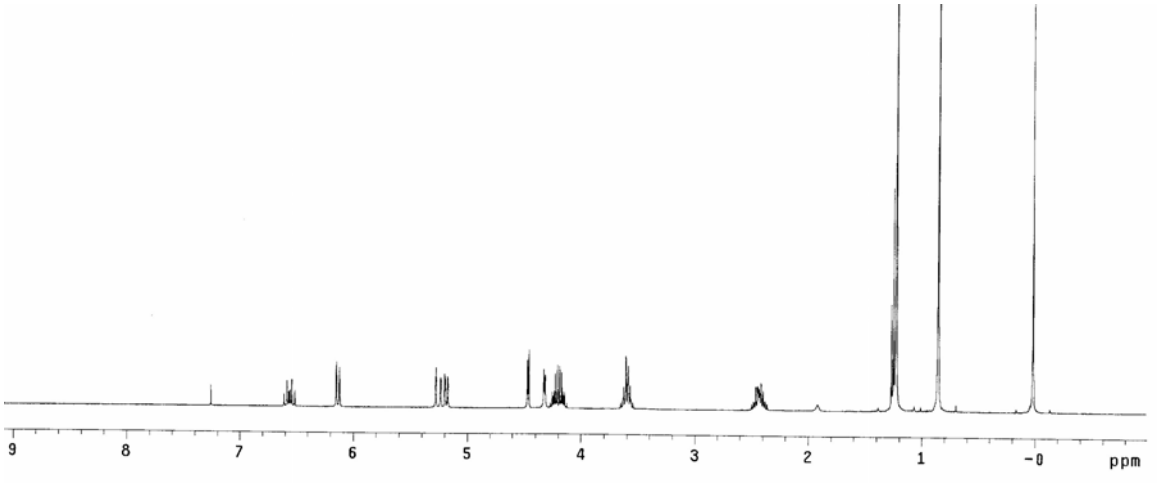
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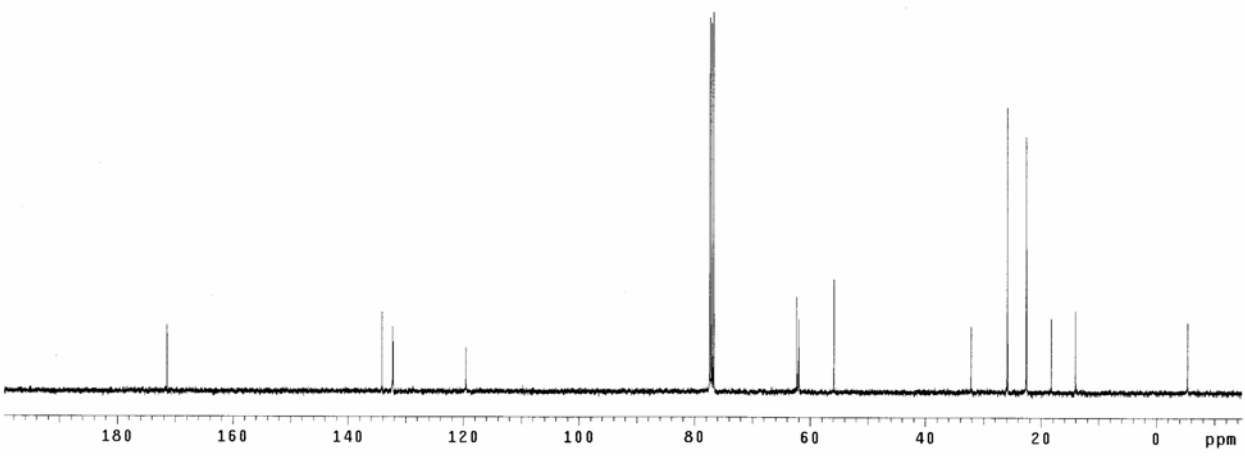
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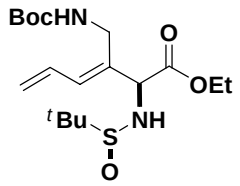
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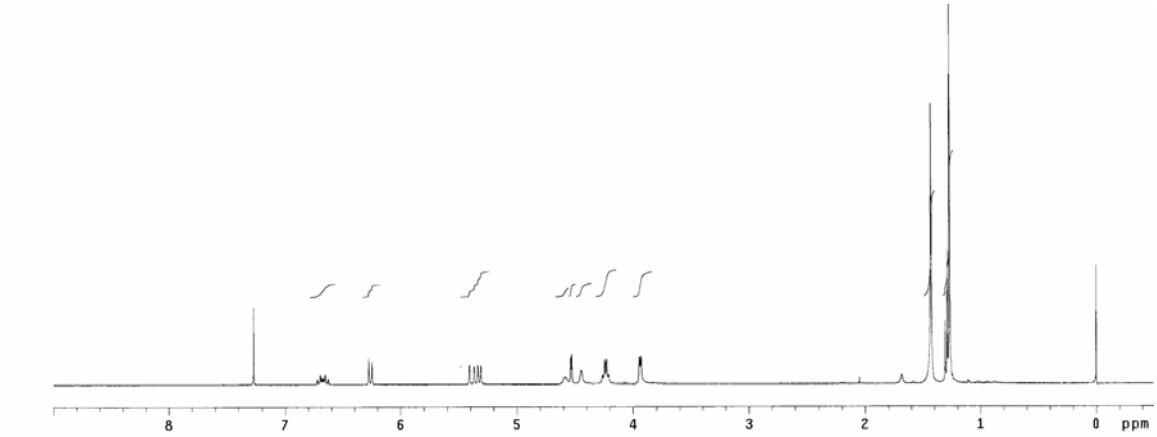
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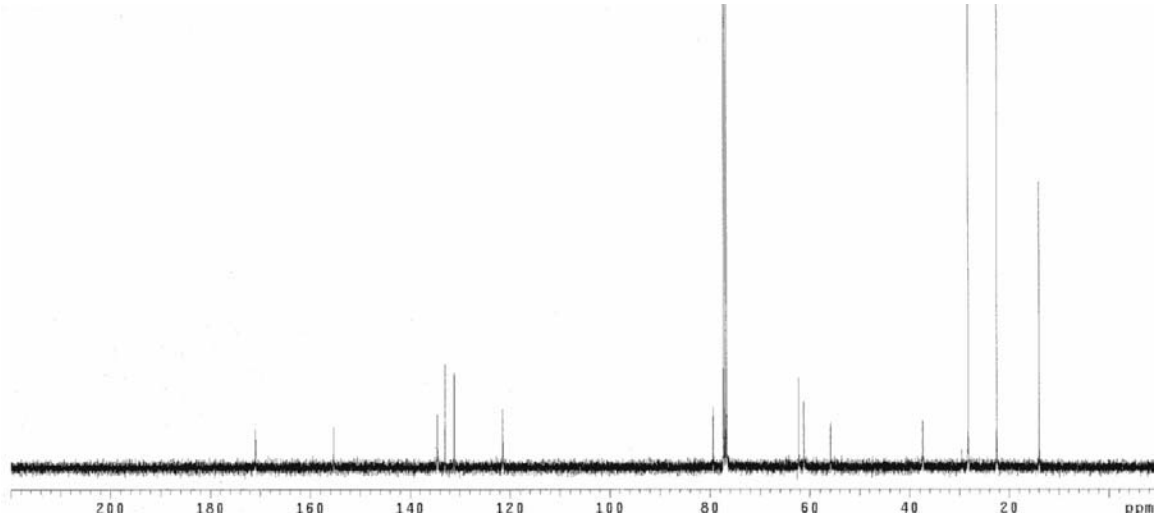
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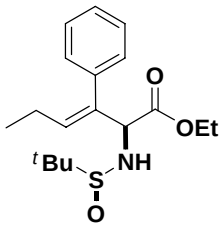
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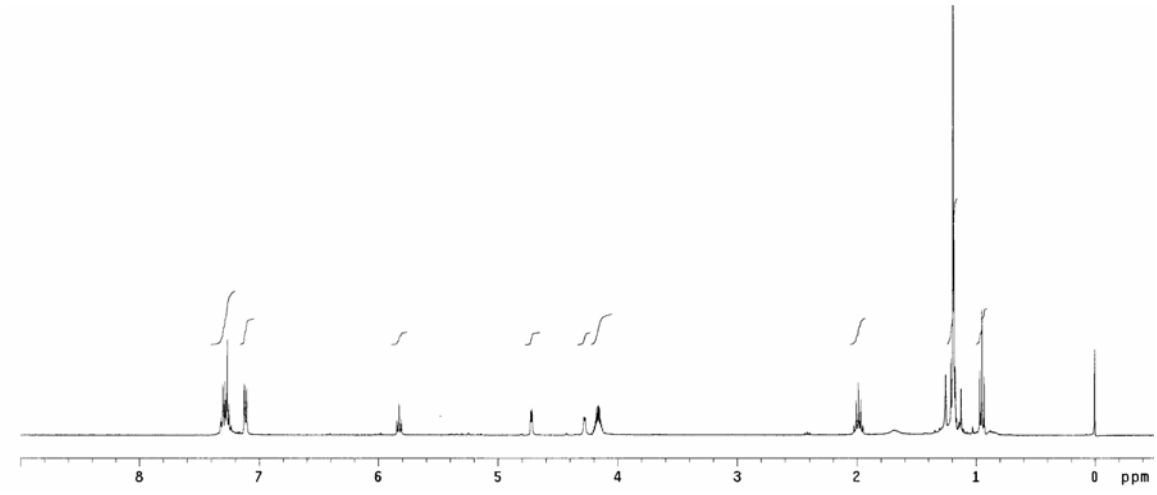
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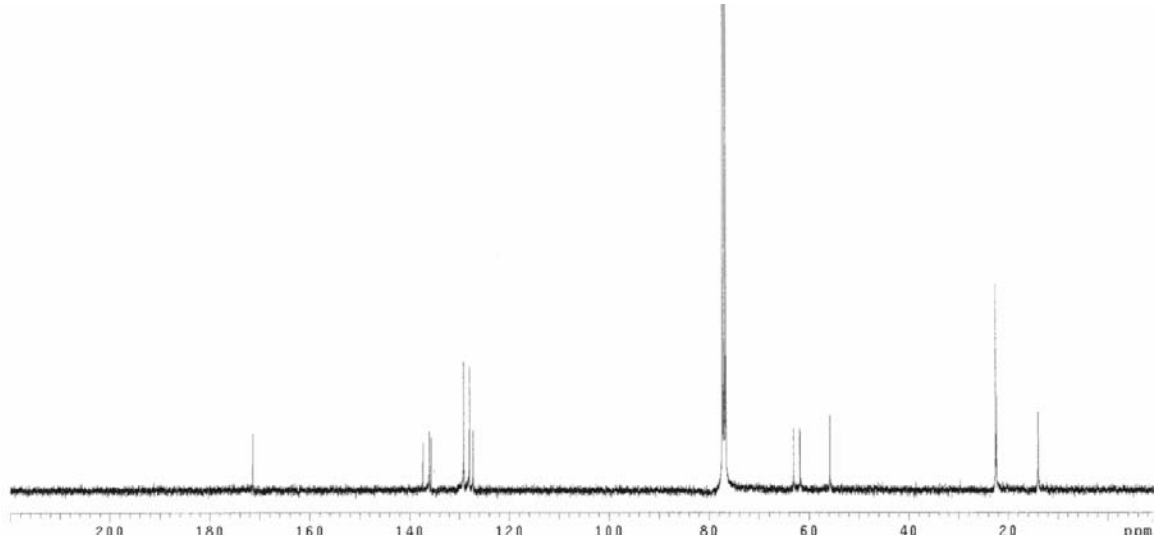
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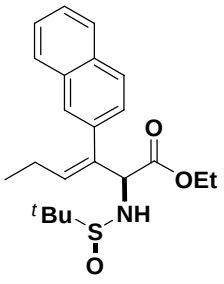
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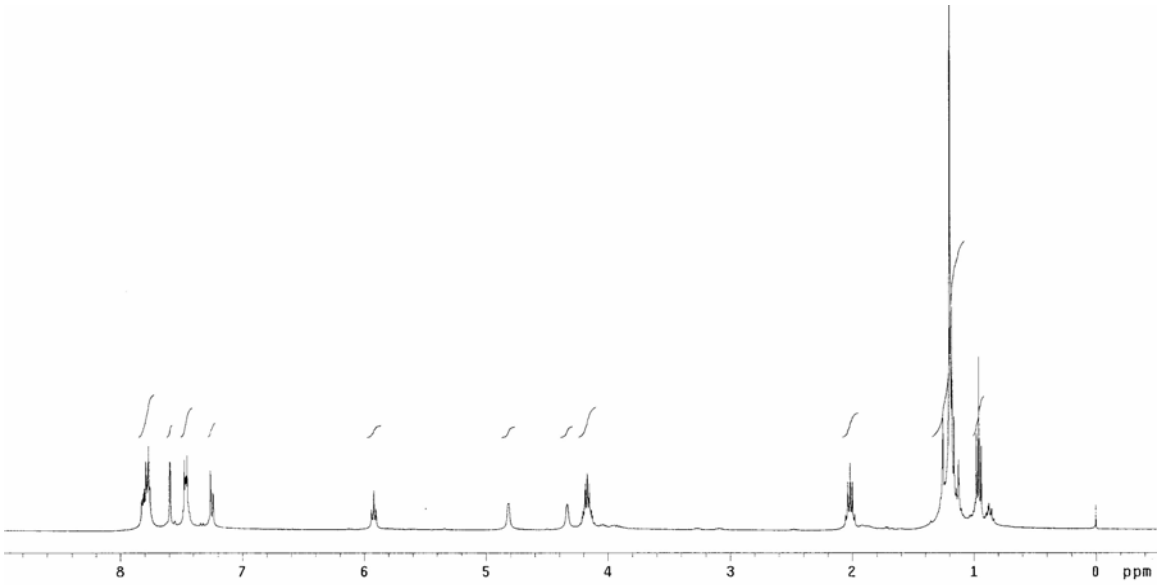
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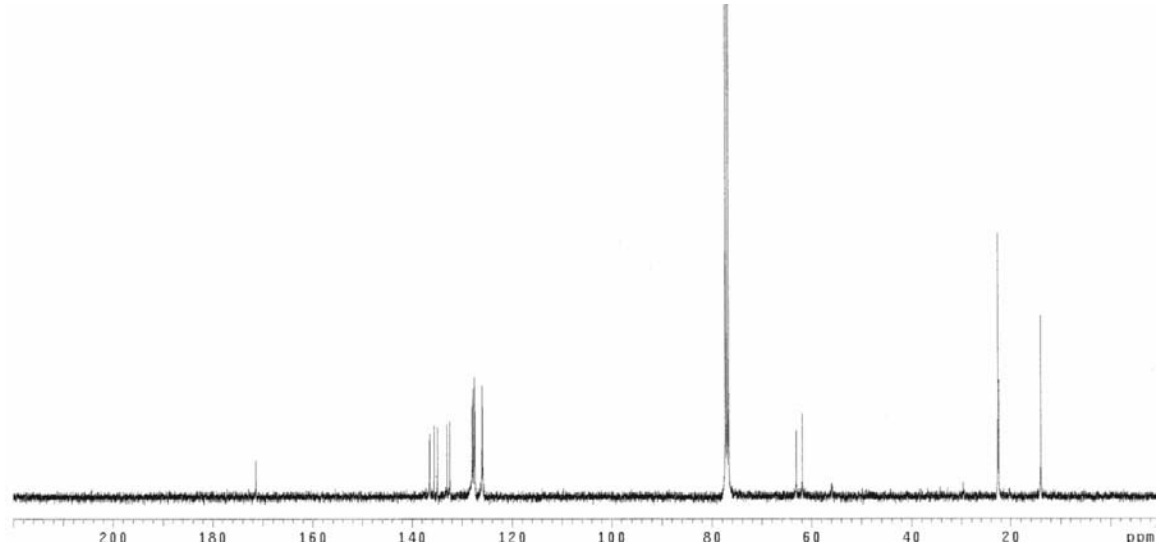
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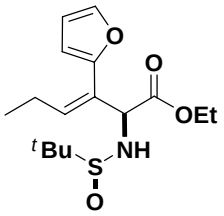
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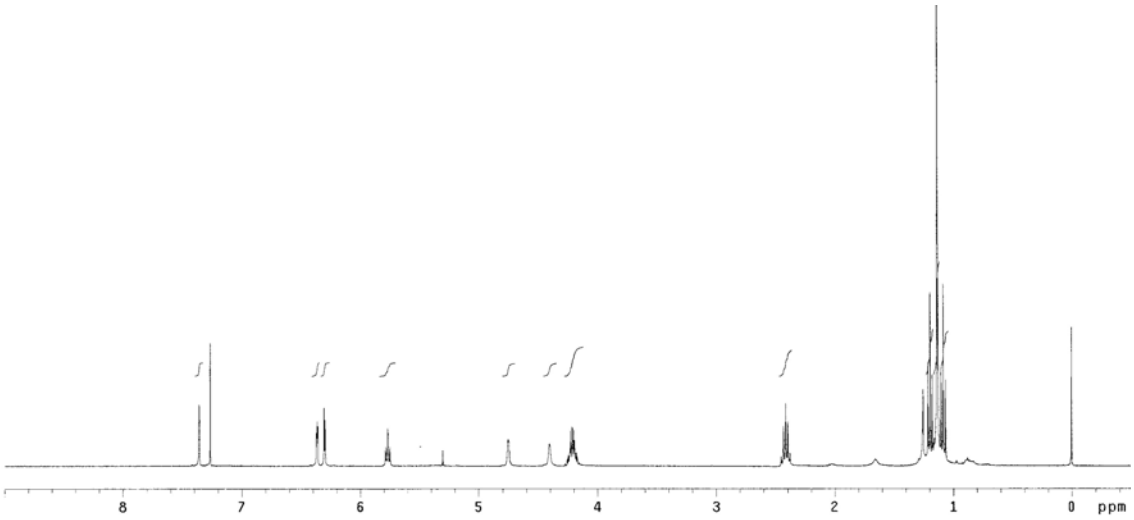
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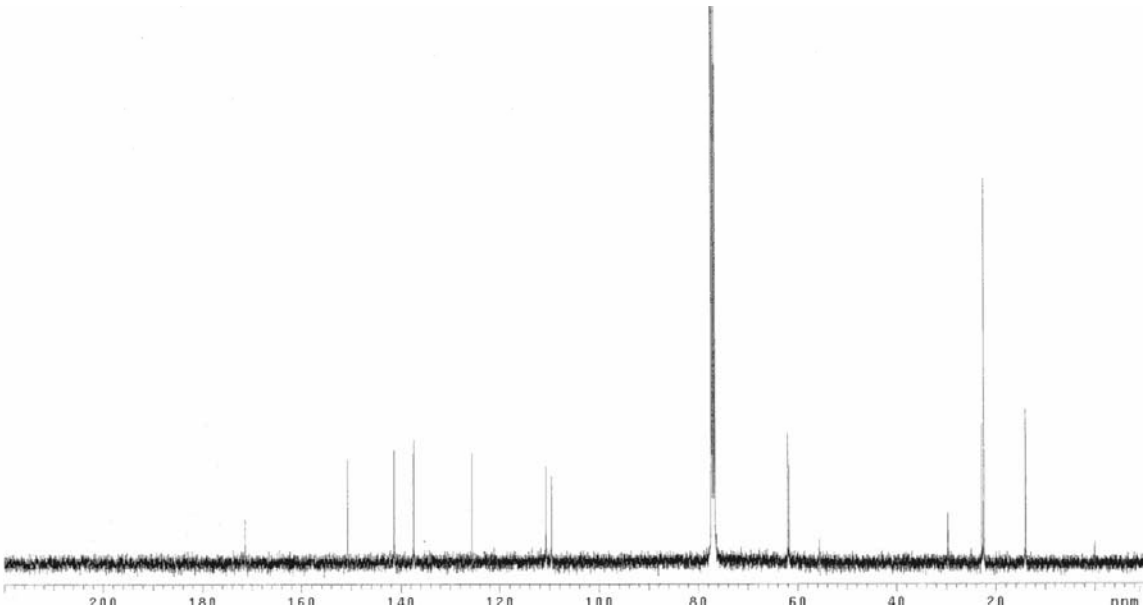
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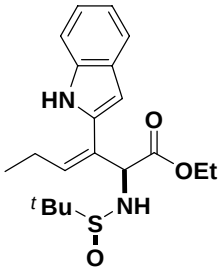
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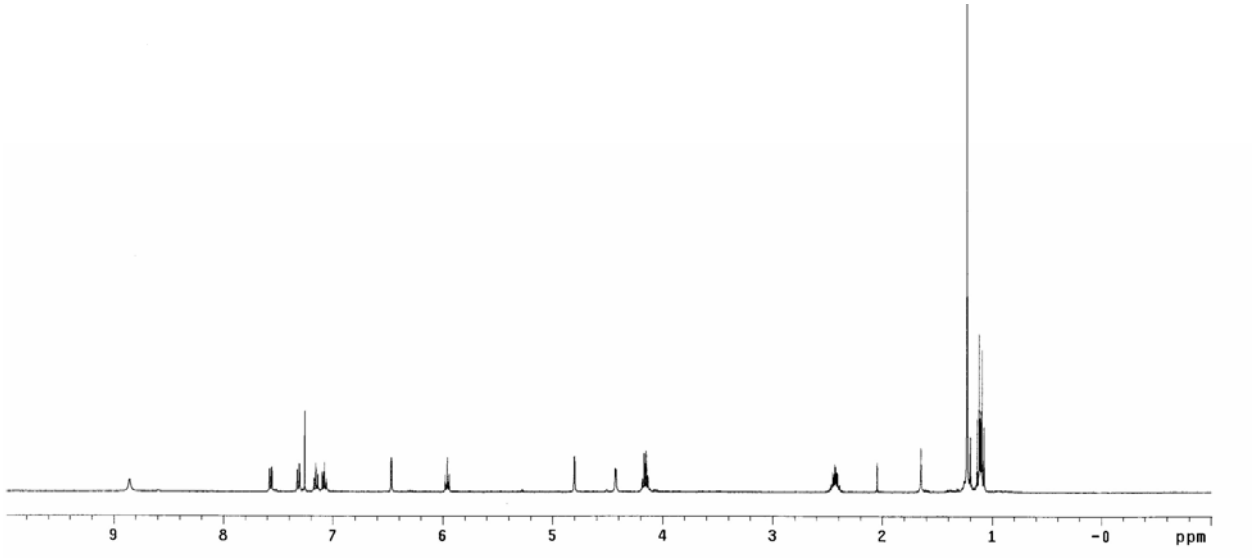
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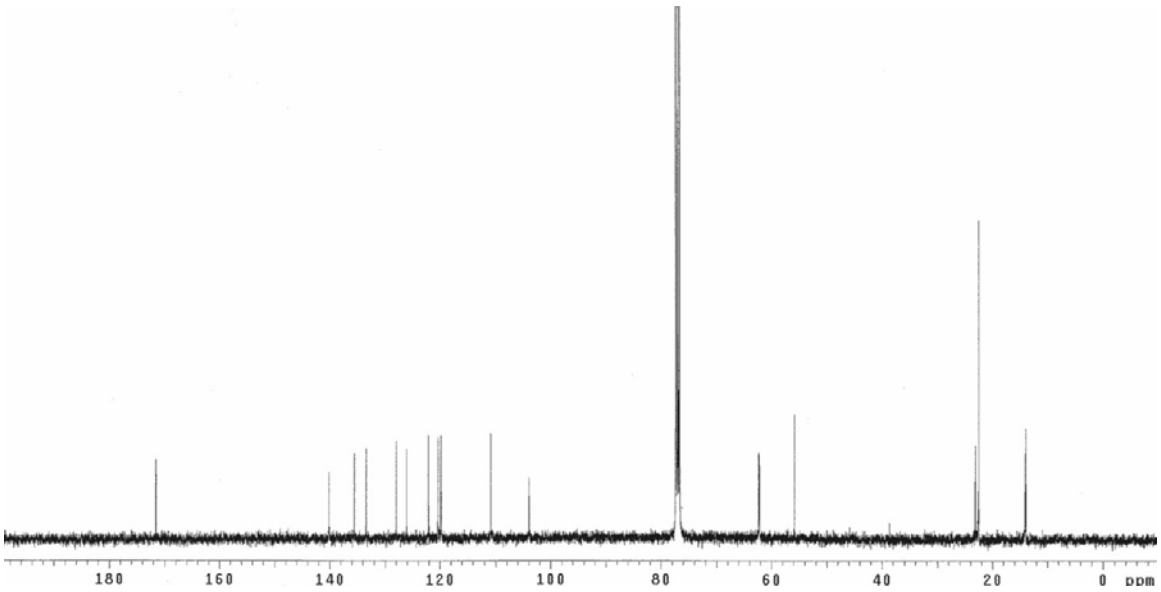
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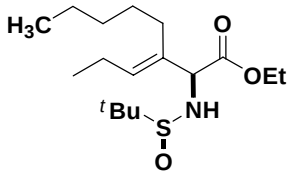
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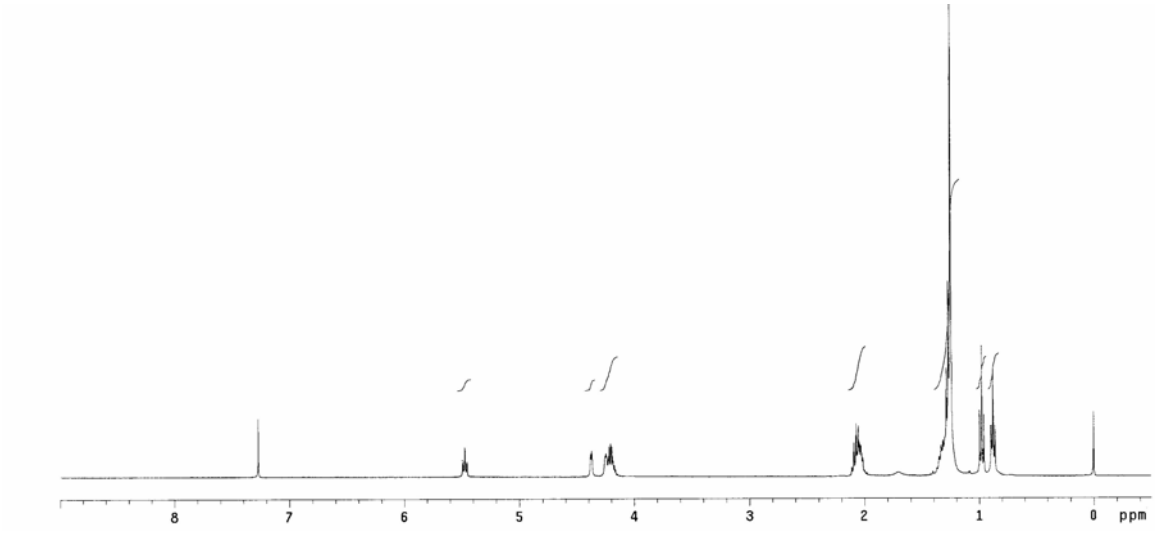
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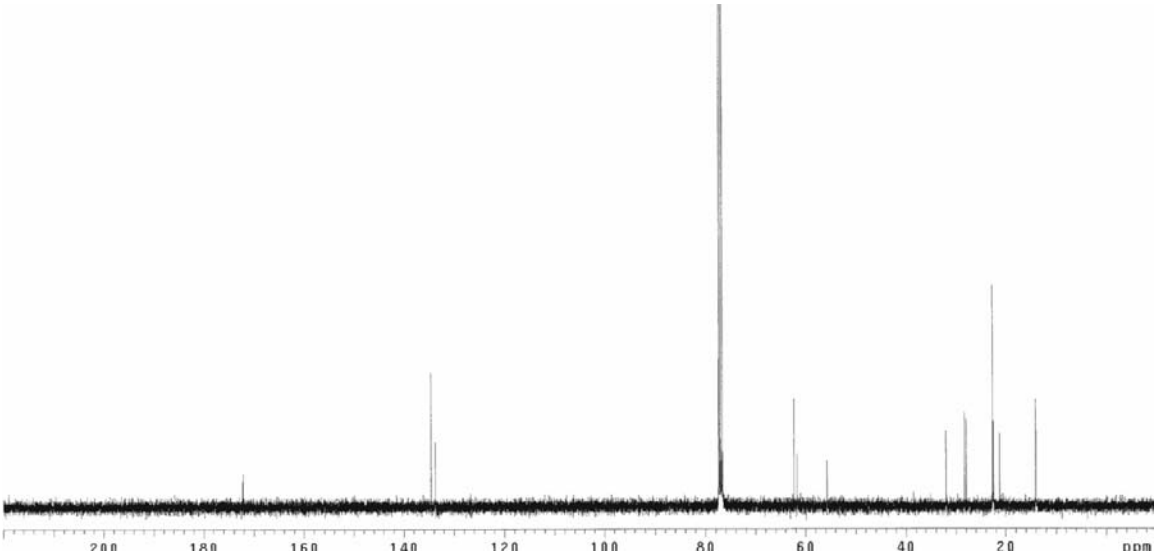
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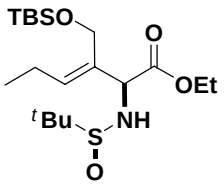
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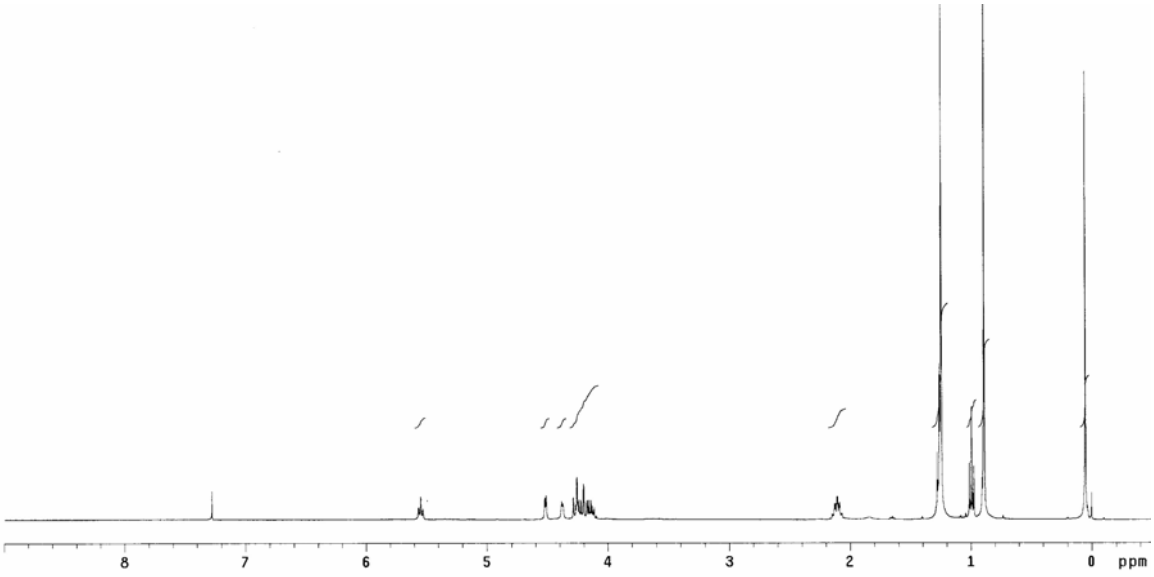
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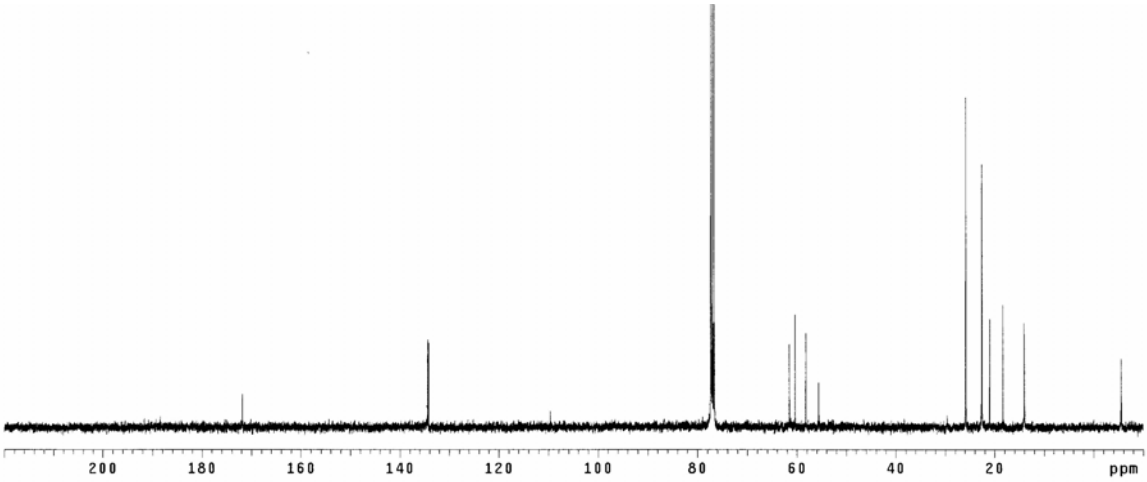
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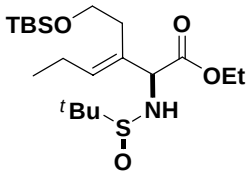
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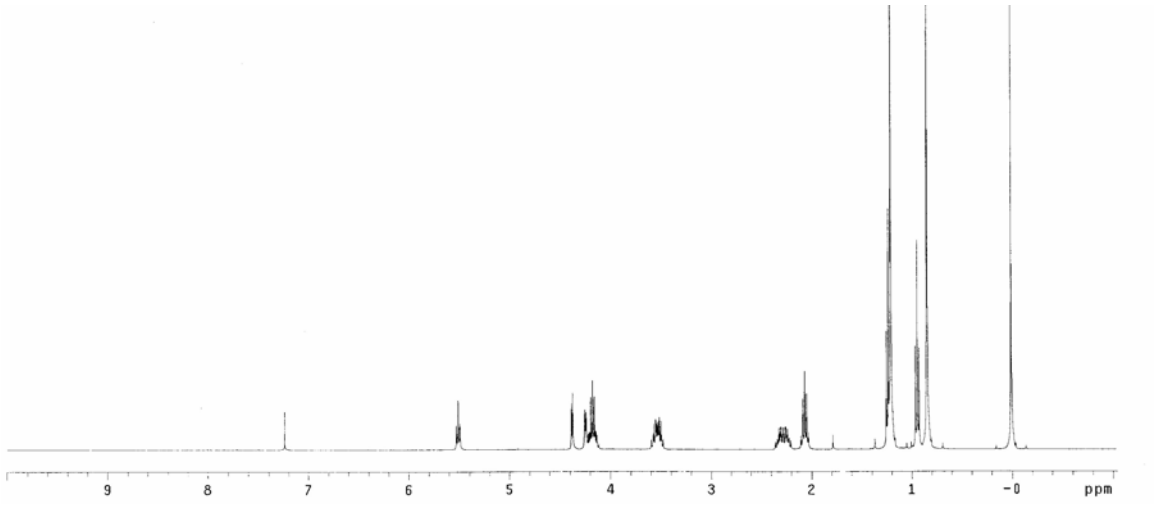
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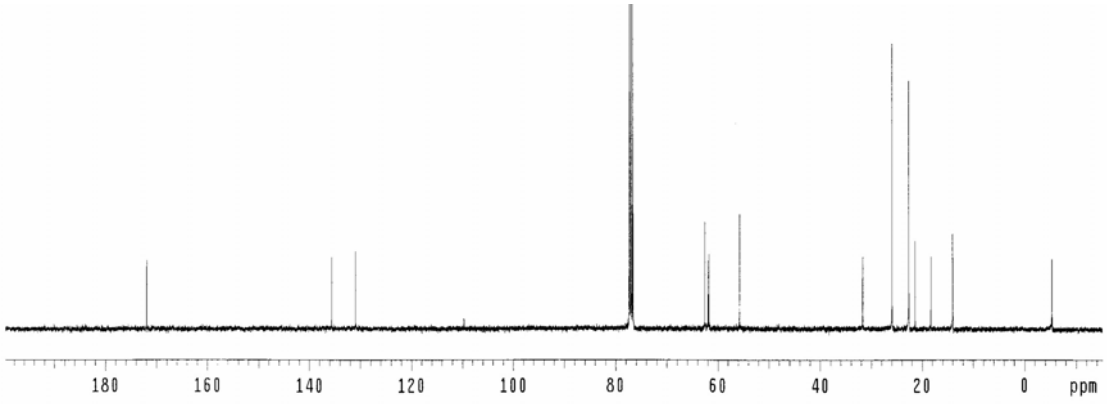
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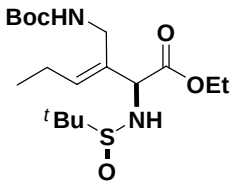
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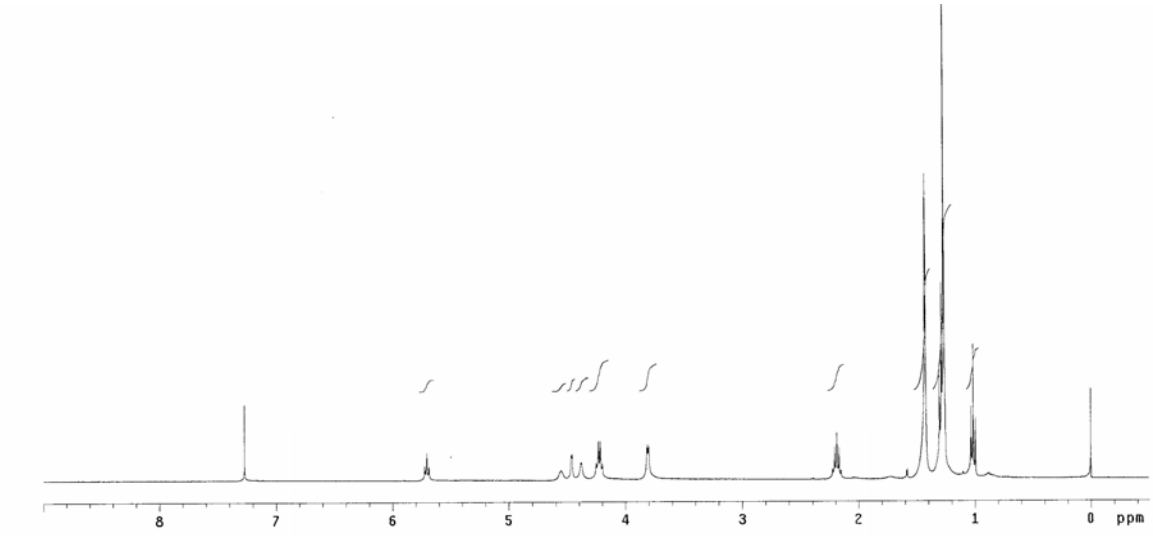
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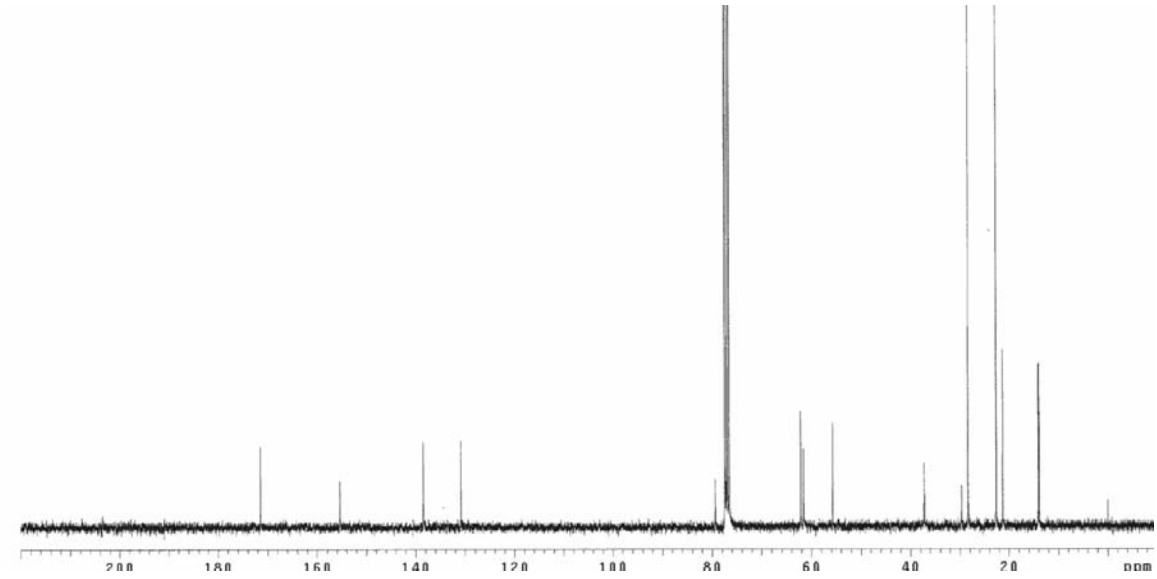
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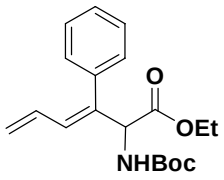
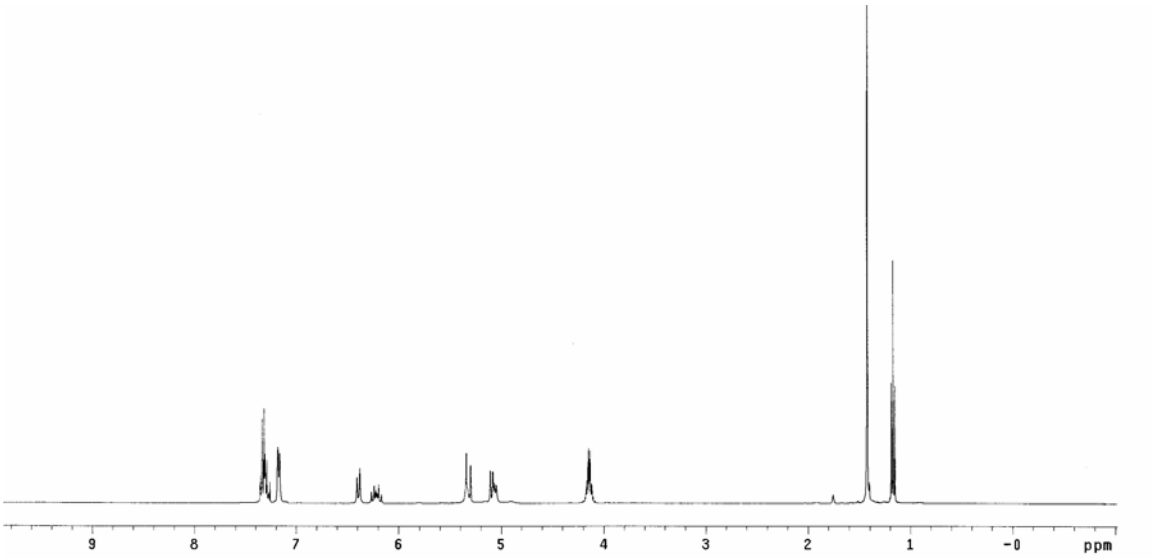
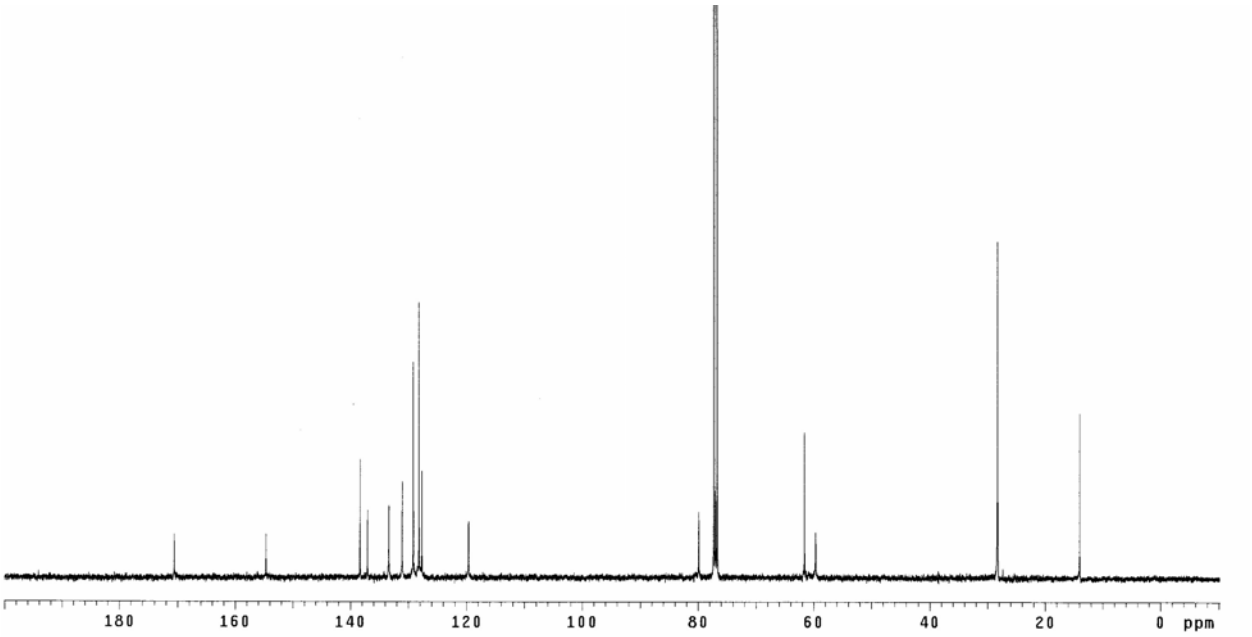
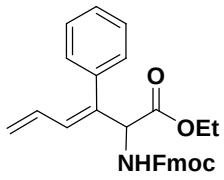


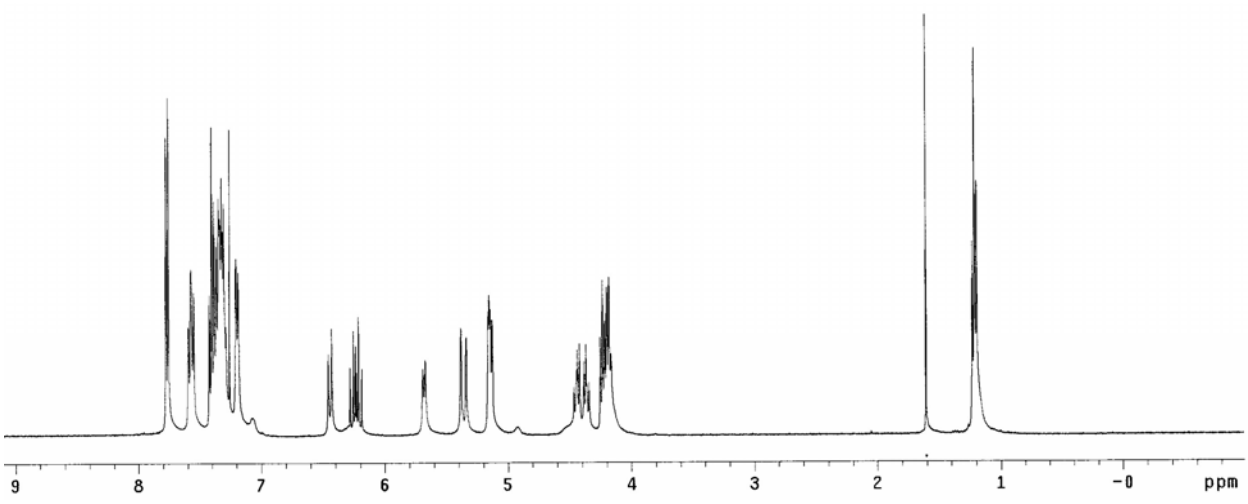
3.19






O
OEt
NHFmoc

3.21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4
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2
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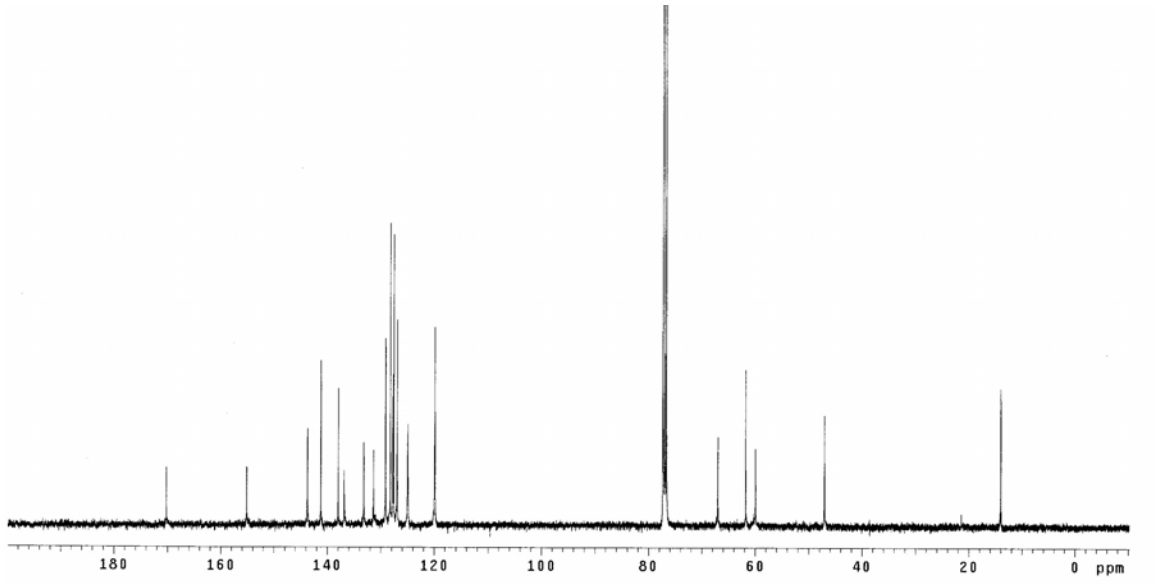
ppm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140
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100
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60
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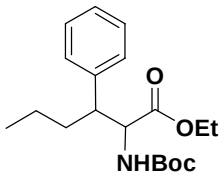
0 ppm



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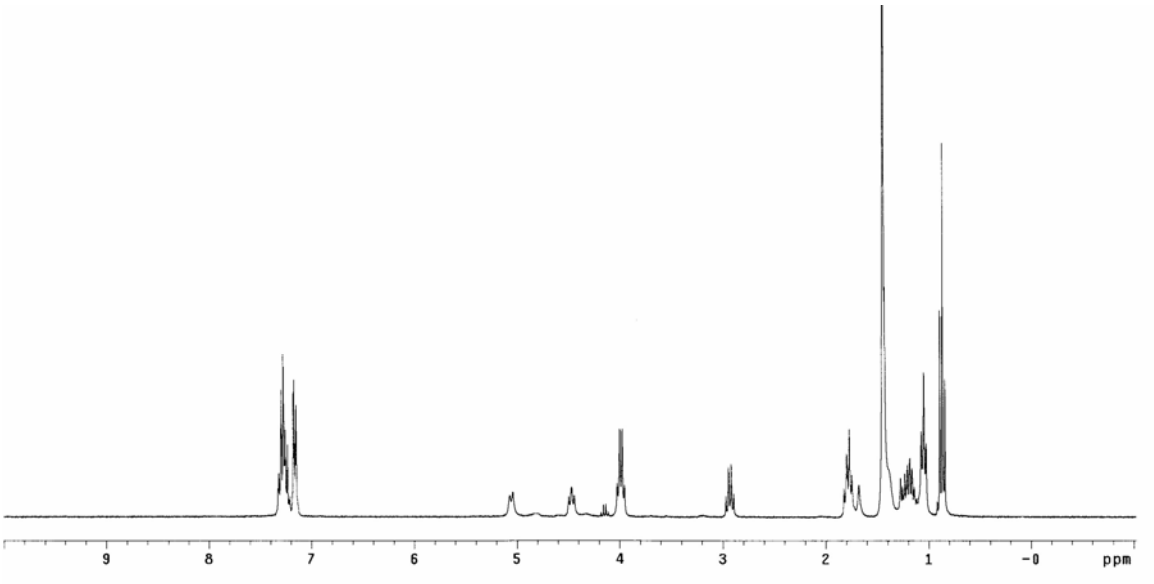
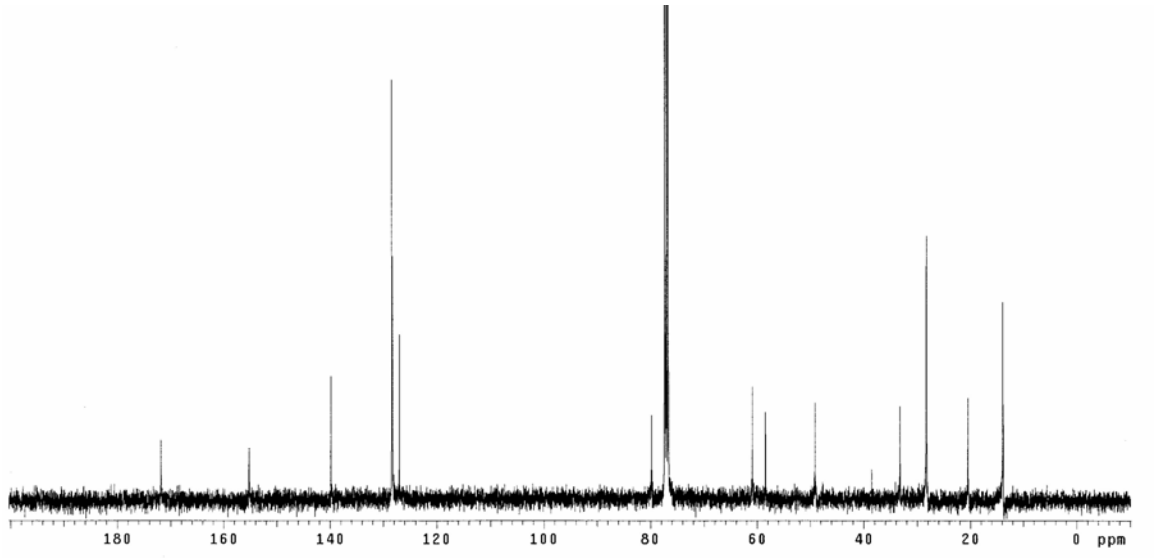
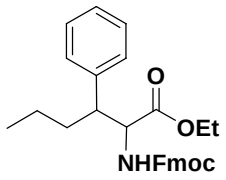
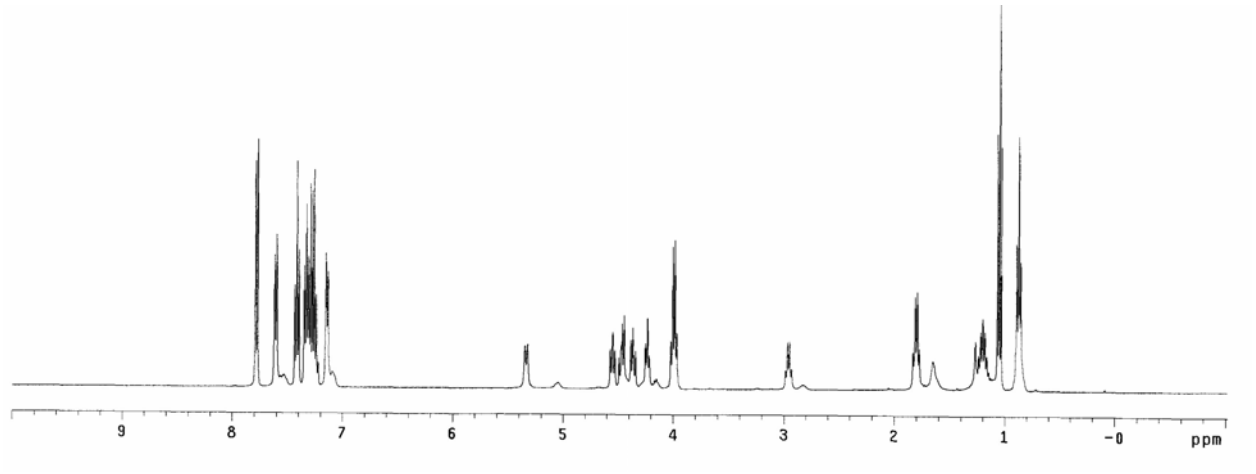





O
OEt
NHFmoc

3.22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-0
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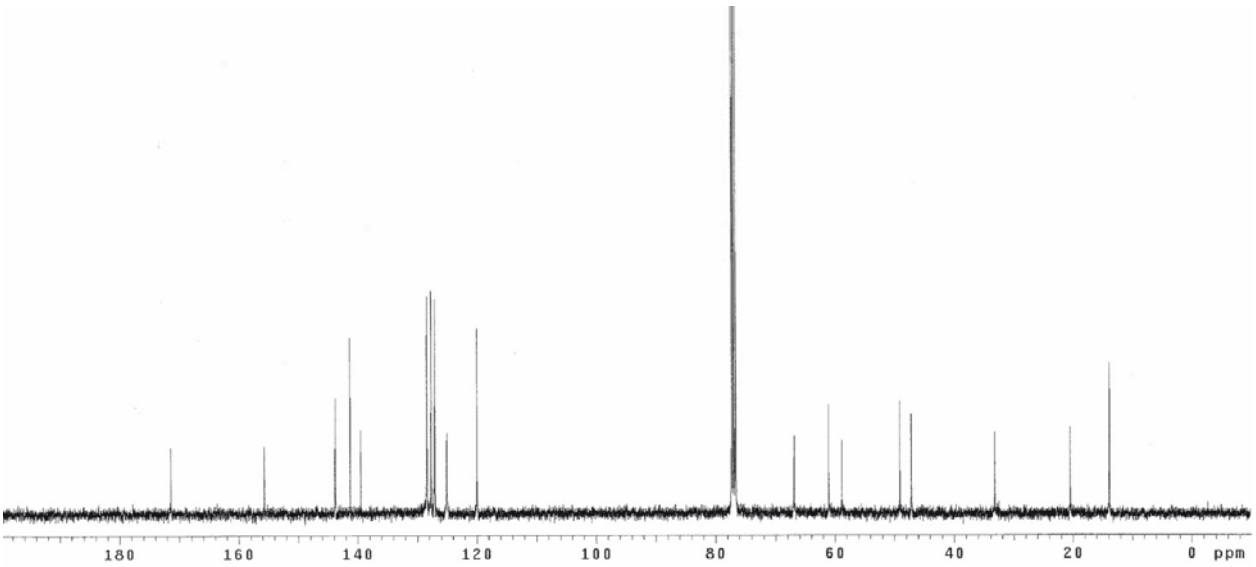
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120
100
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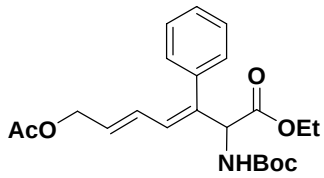
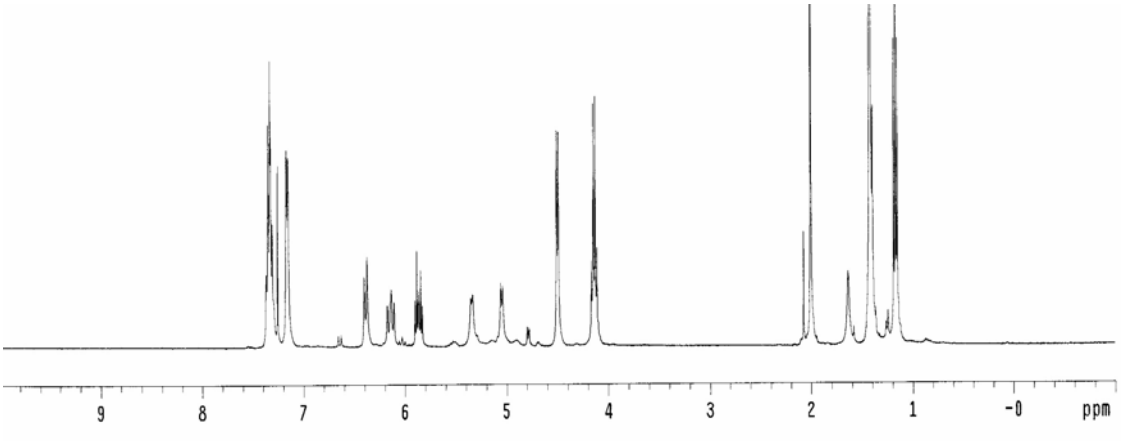
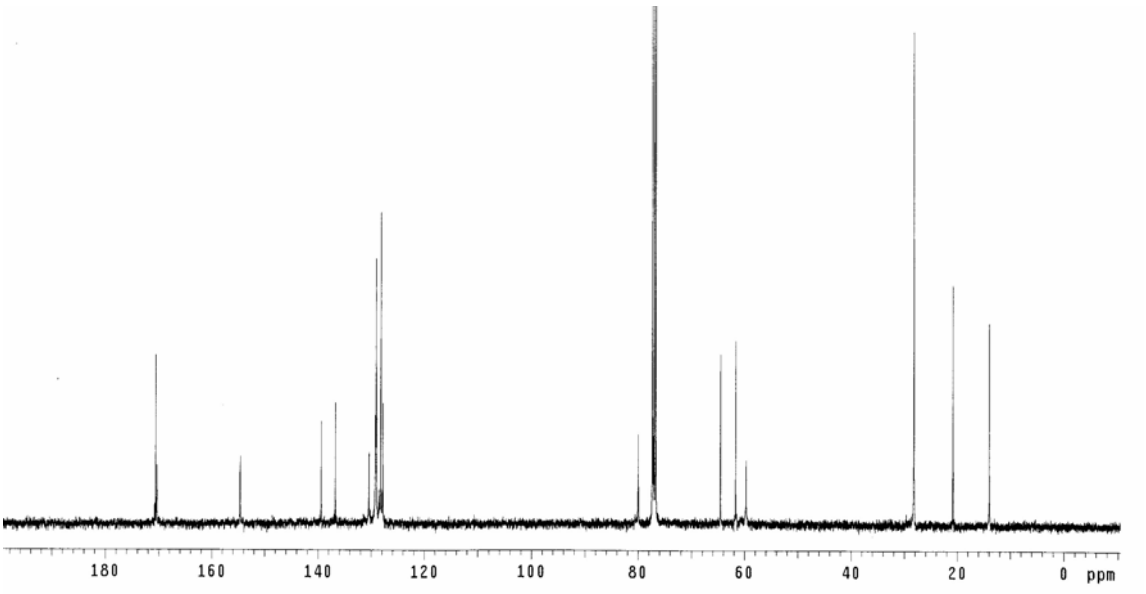
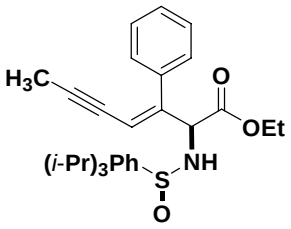
20
0 ppm



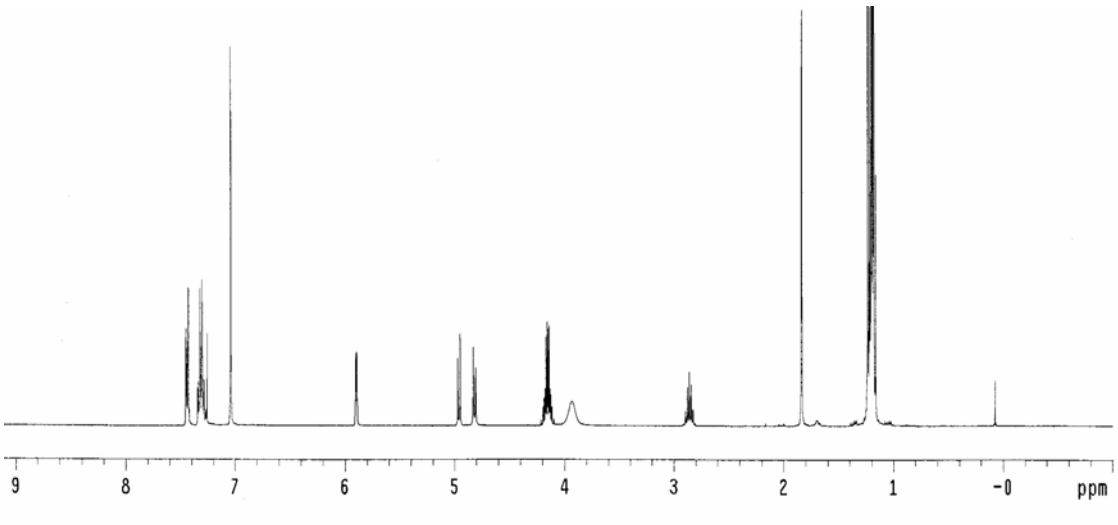
3.23
(mixture of two diastereomers)






H3C
O
OEt
(i-Pr)3Ph
NH
S
O

3.27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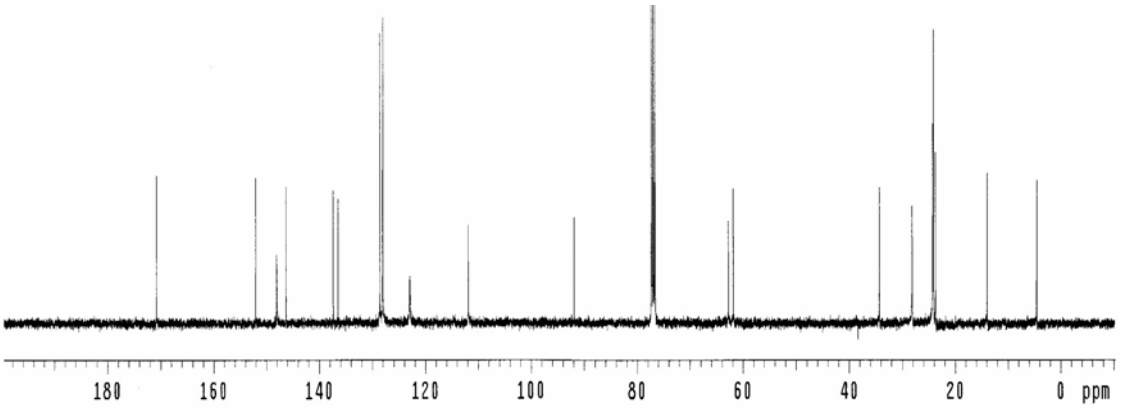
7
6
5
4
3
2
1
-0
ppm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100
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60
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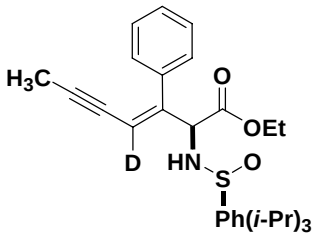
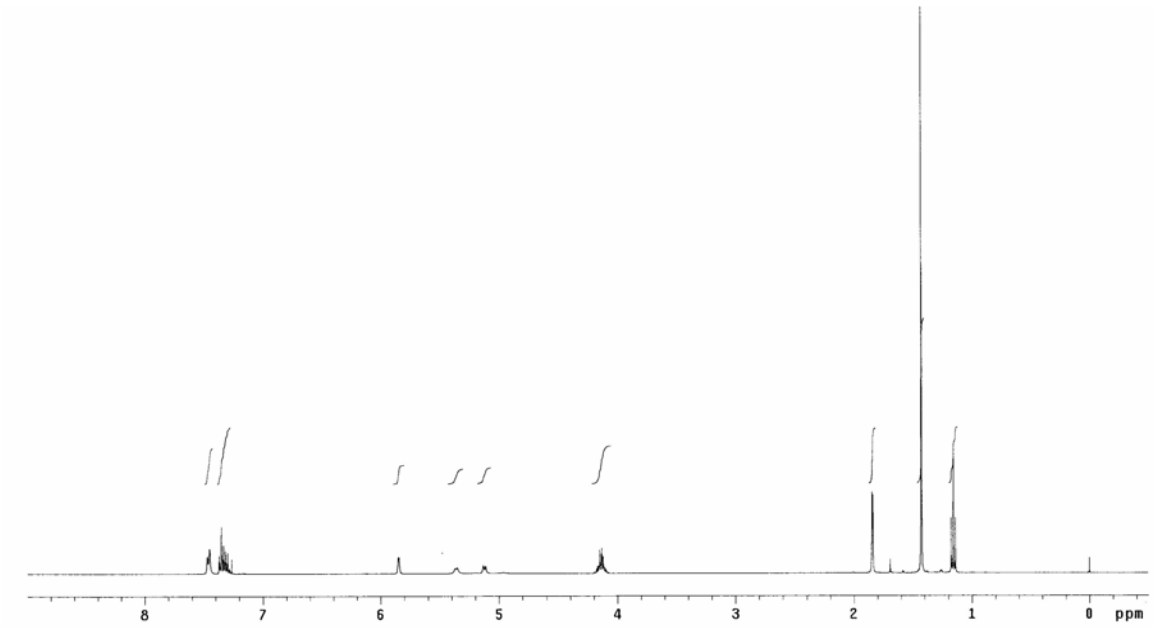
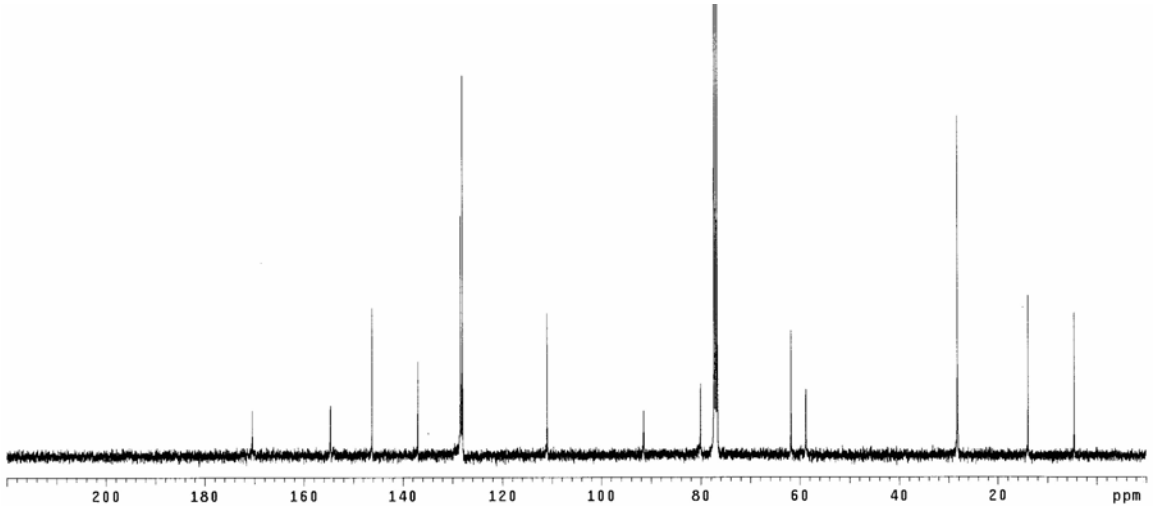
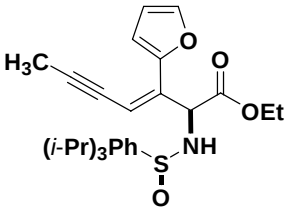
20
0 ppm



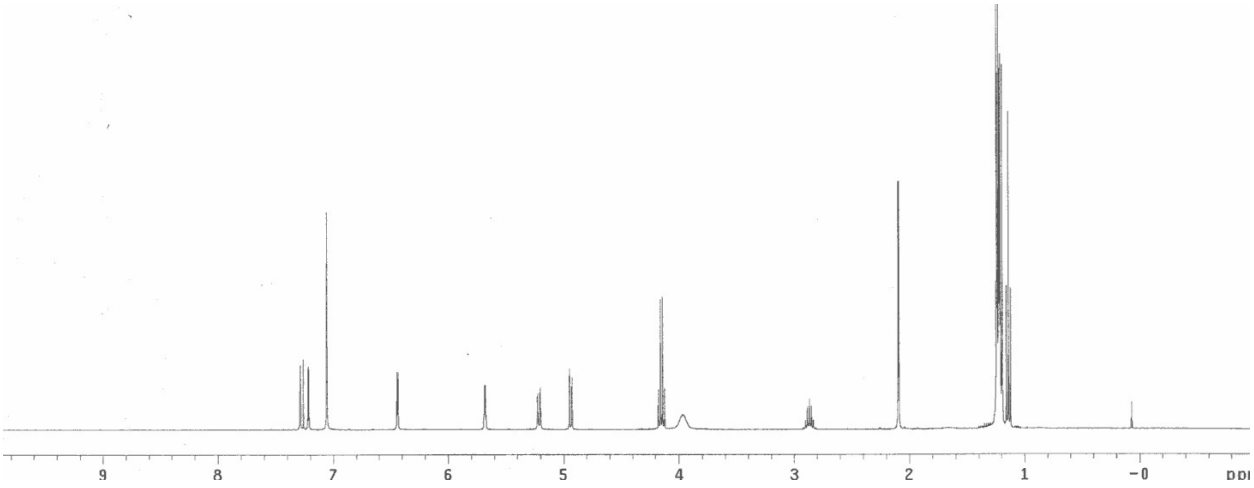
***deuterio*-3.27**






H3C
O
O
OEt
(i-Pr)3Ph
S
NH
O

3.28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5
4
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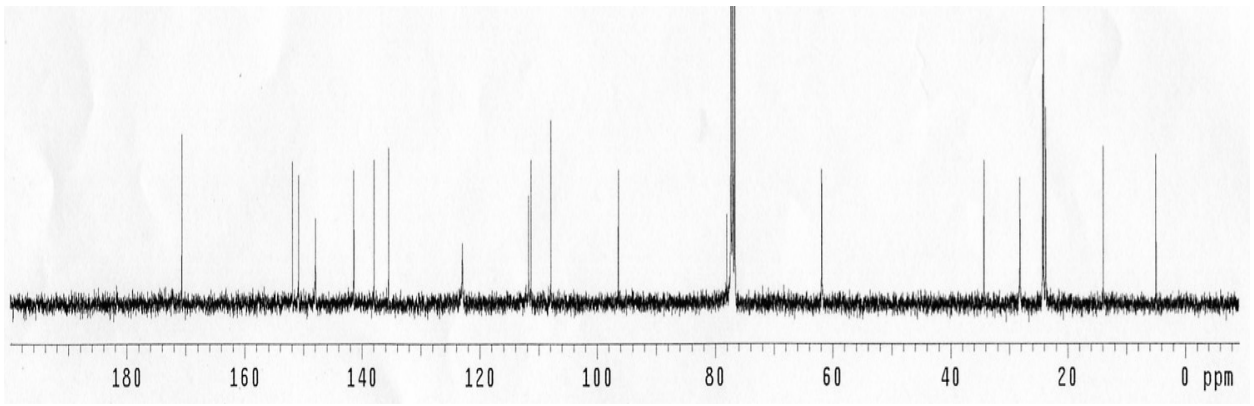
1
−0
PPI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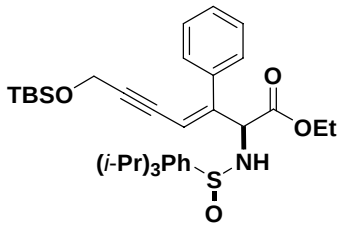
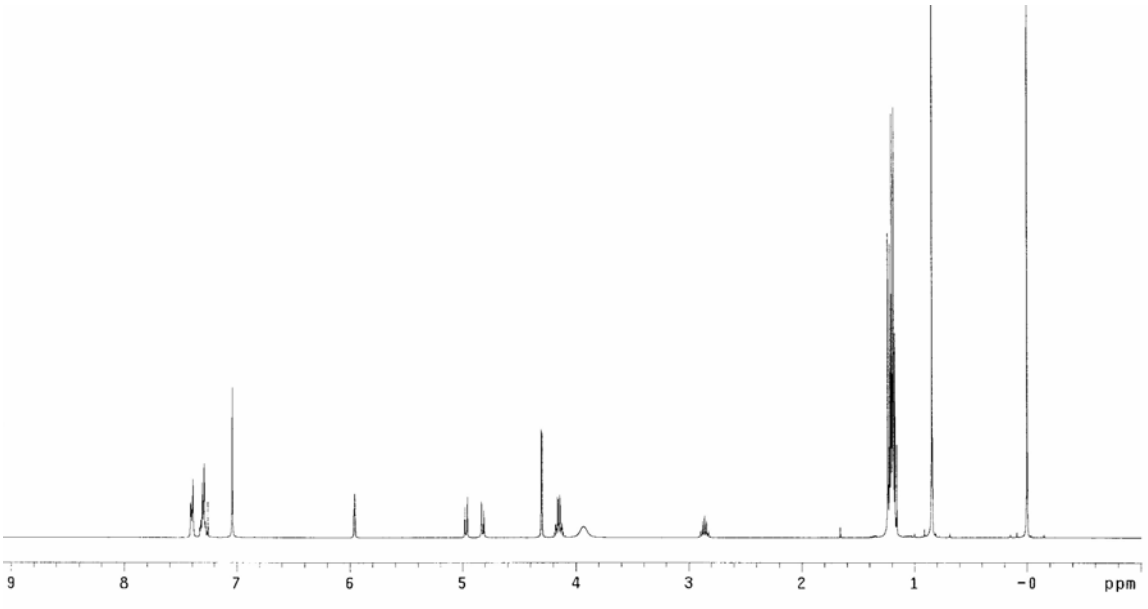

TBSO
O
OEt
(i-Pr)3Ph
NH
S
O

3.29


9
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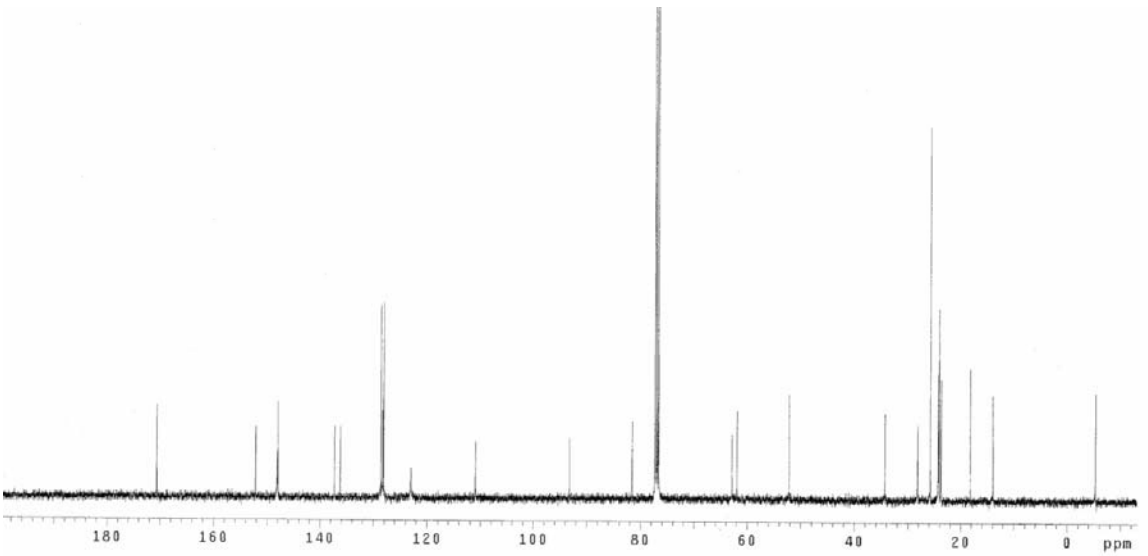
7
6
5
4
3
2
1
-0
ppm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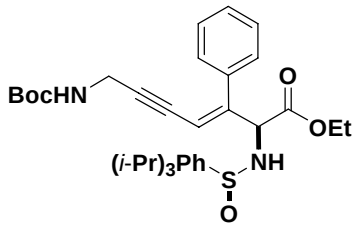
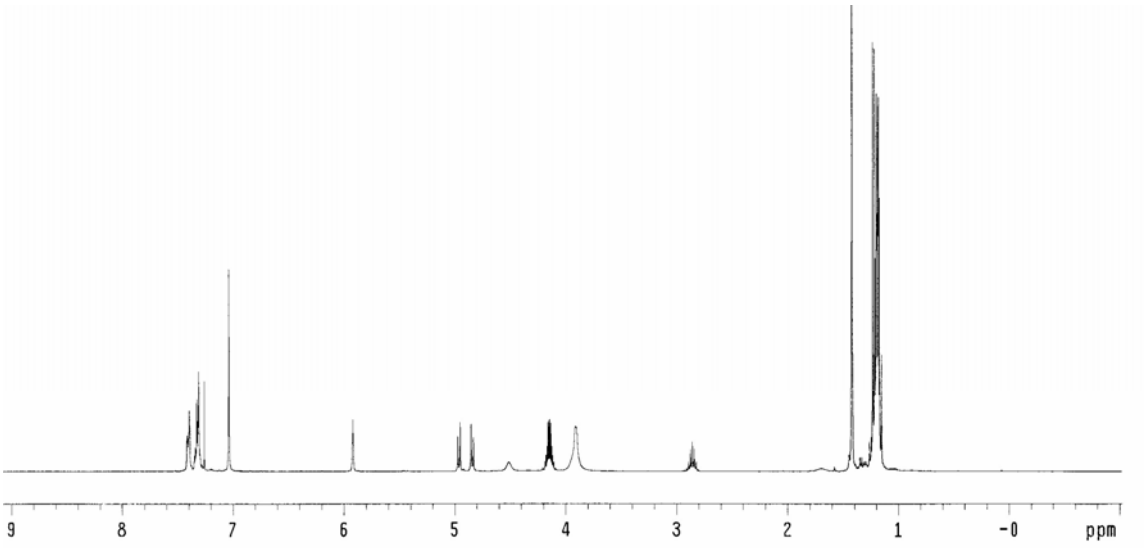
120
100
80
60
40
20
0
ppm


BocHN
O
OEt
(i-Pr)3Ph
S
NH
O

3.30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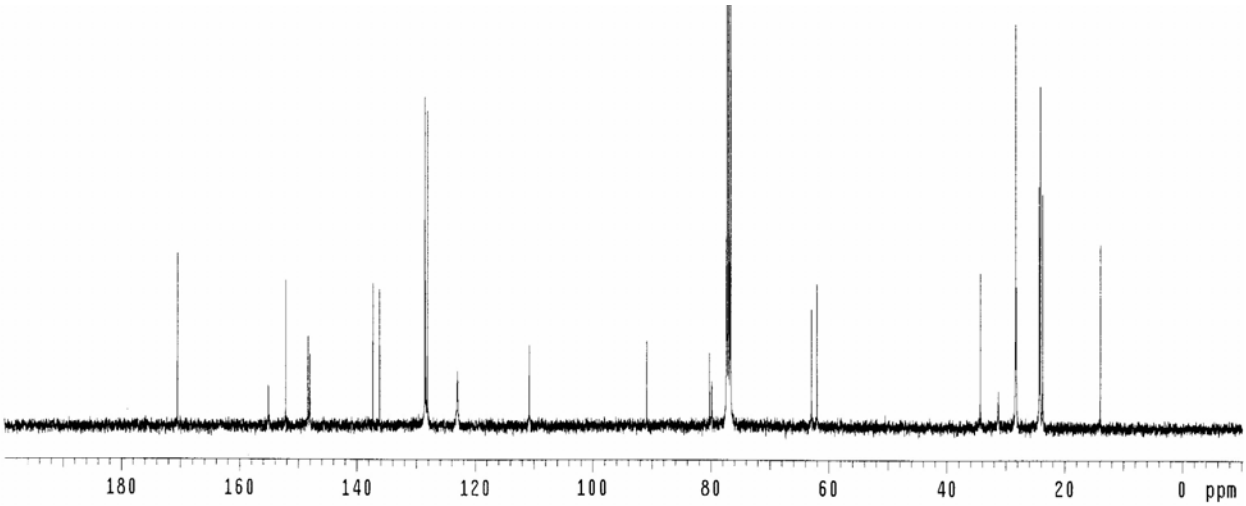
6
5
4
3
2
1
-0
ppm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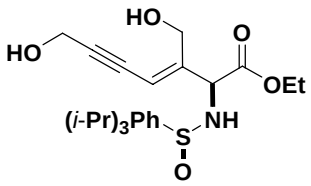
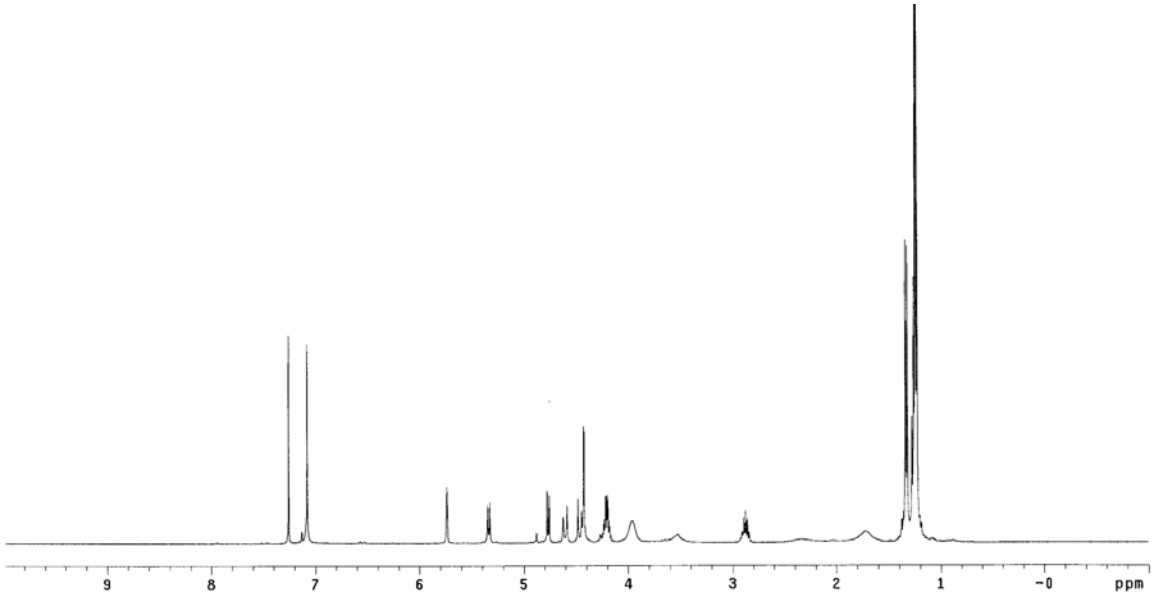
140
120
100
80
60
40
20
0
ppm


HO
HO
O
OEt
(i-Pr)3Ph
S
NH
O

3.32


9
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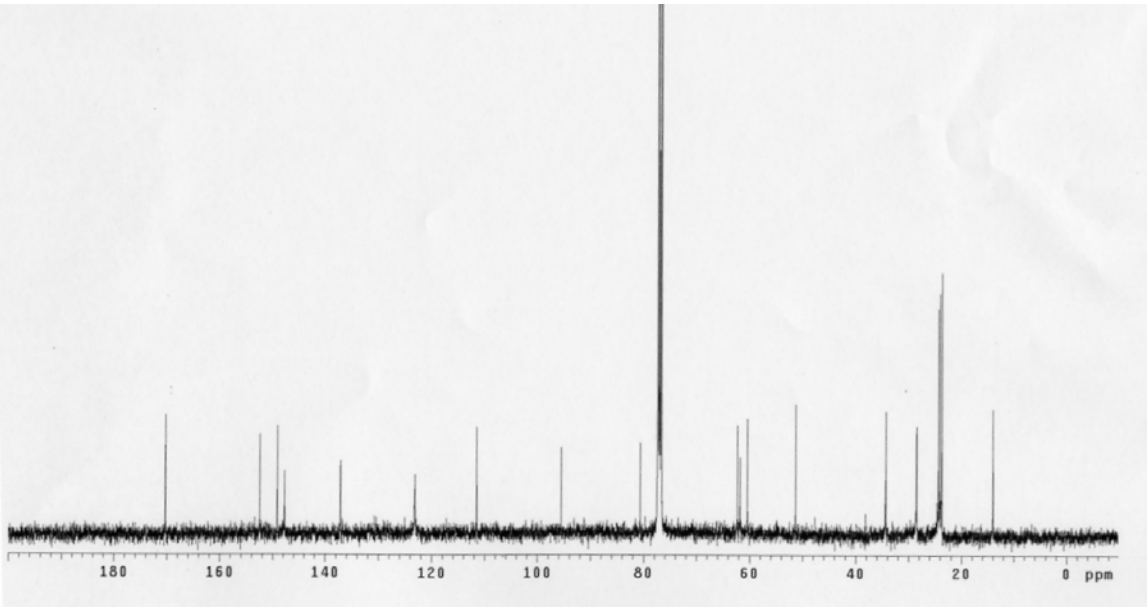
7
6
5
4
3
2
1
-0
ppm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120
100
80
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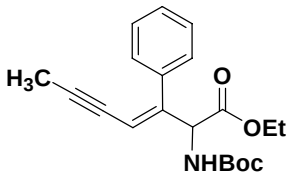
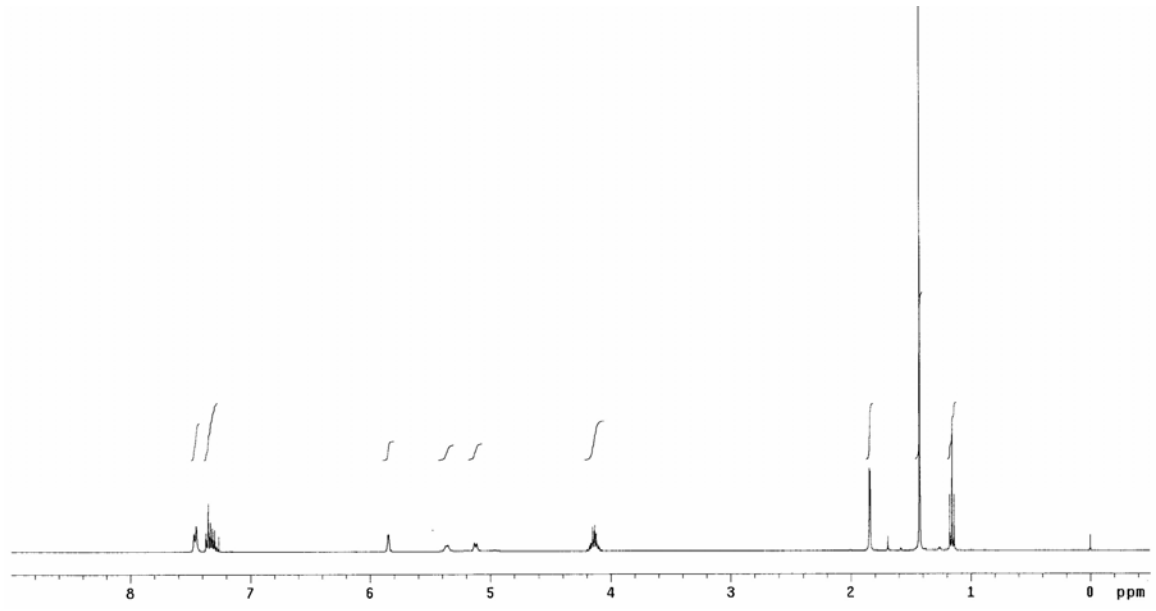
40
20
0 ppm


H3C
O
OEt
NHBoc

3.33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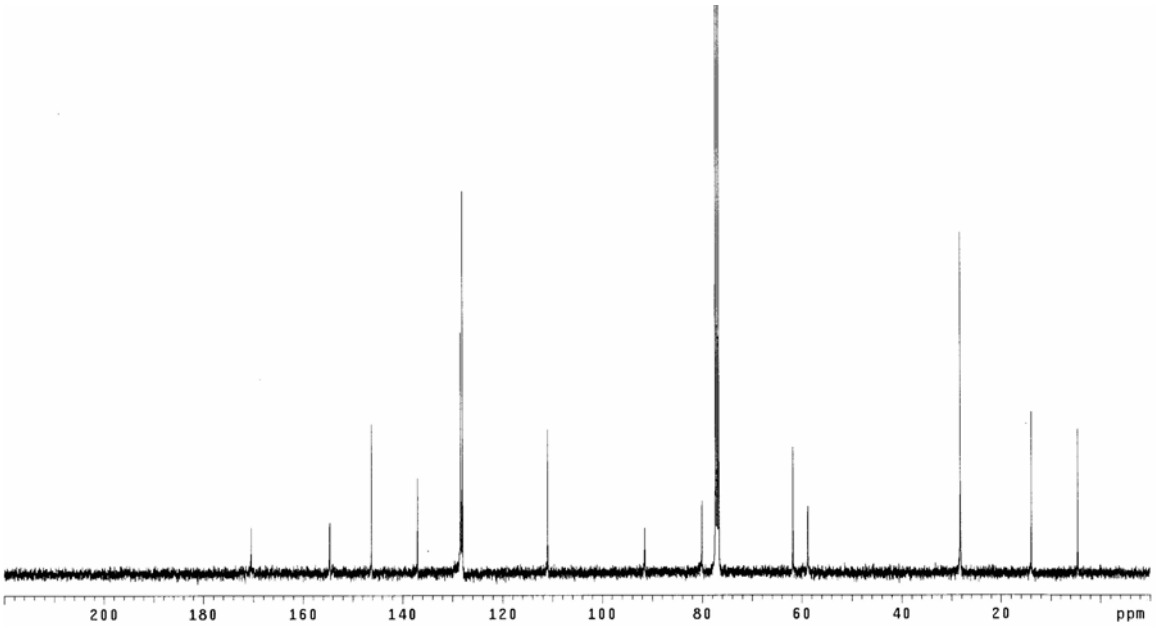
4
3
2
1
0
ppm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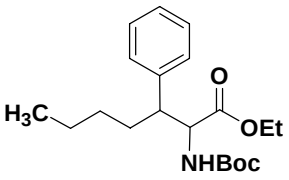
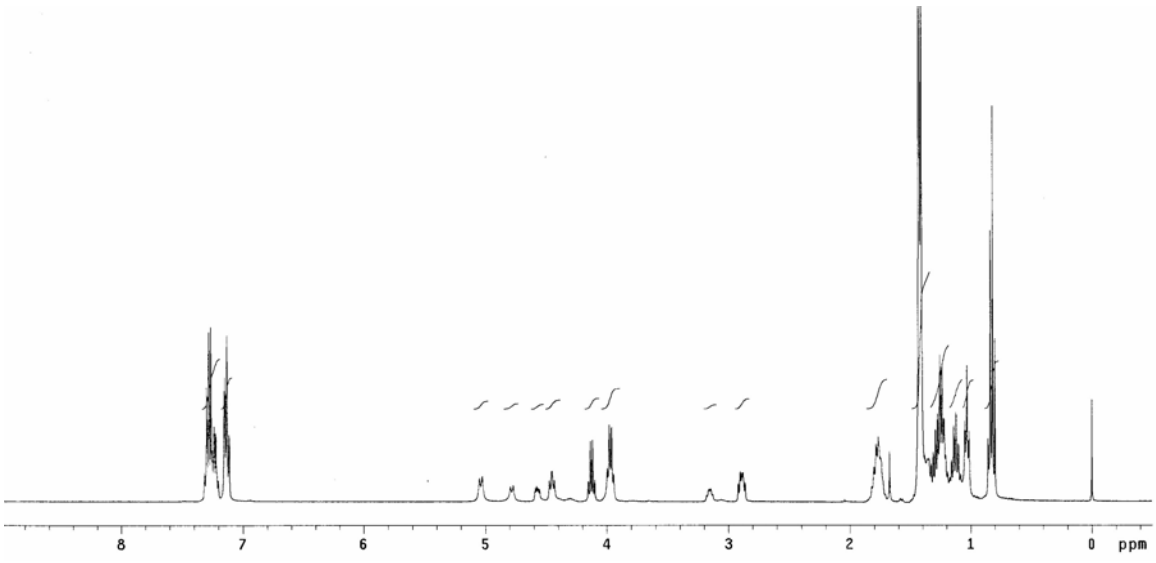
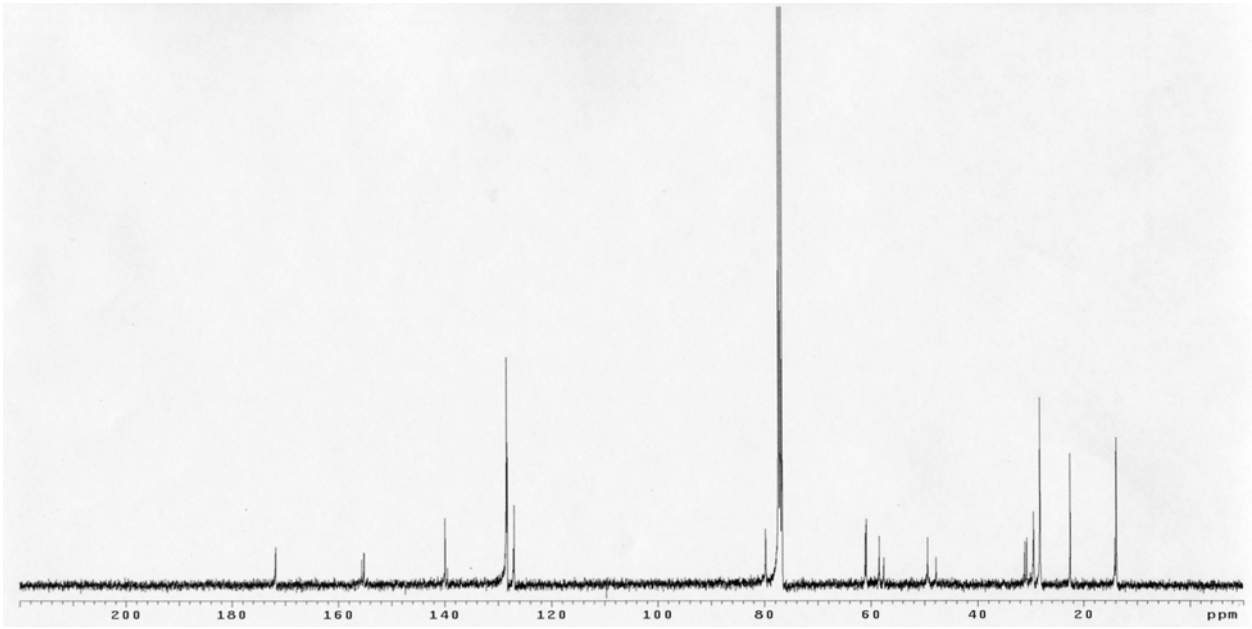
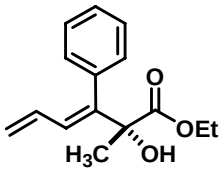
120
100
80
60
40
20
ppm



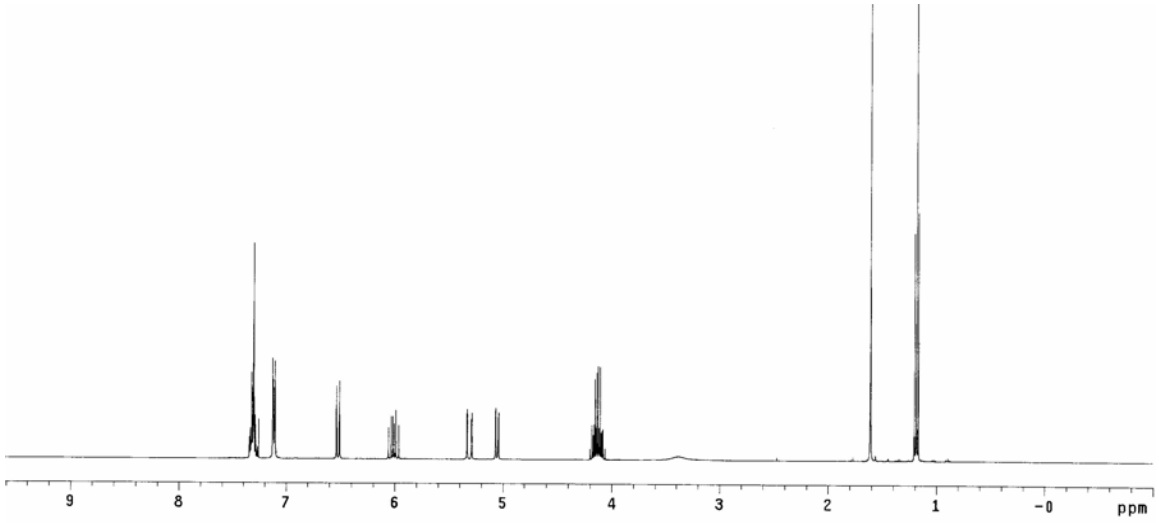
3.34
(mixture of two diastereomers)

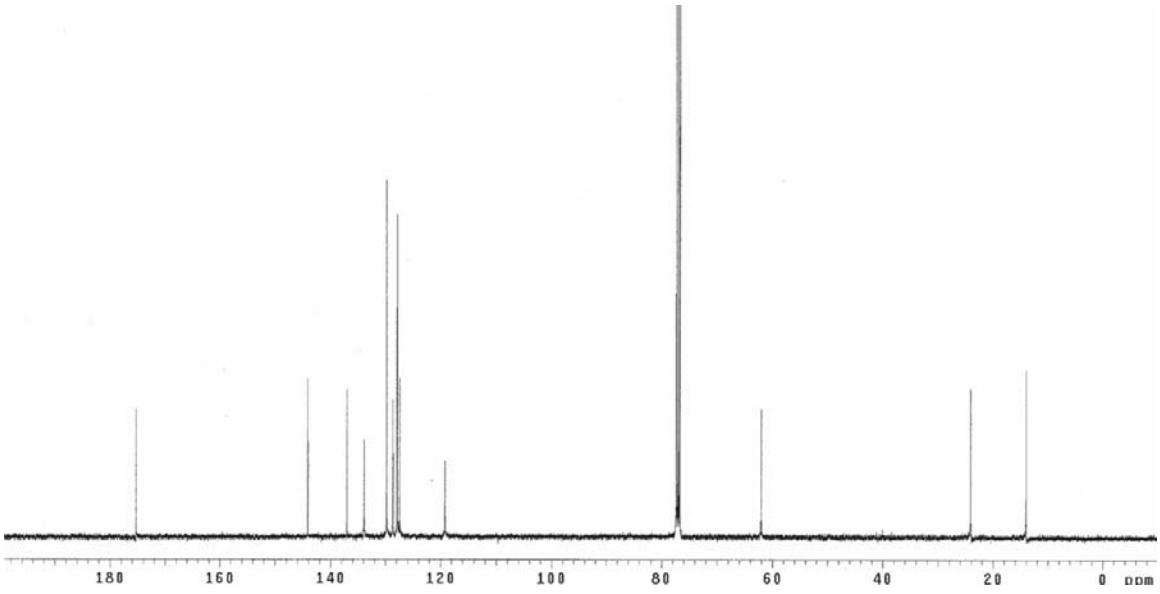


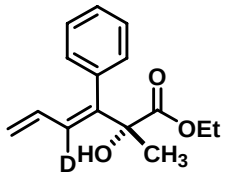




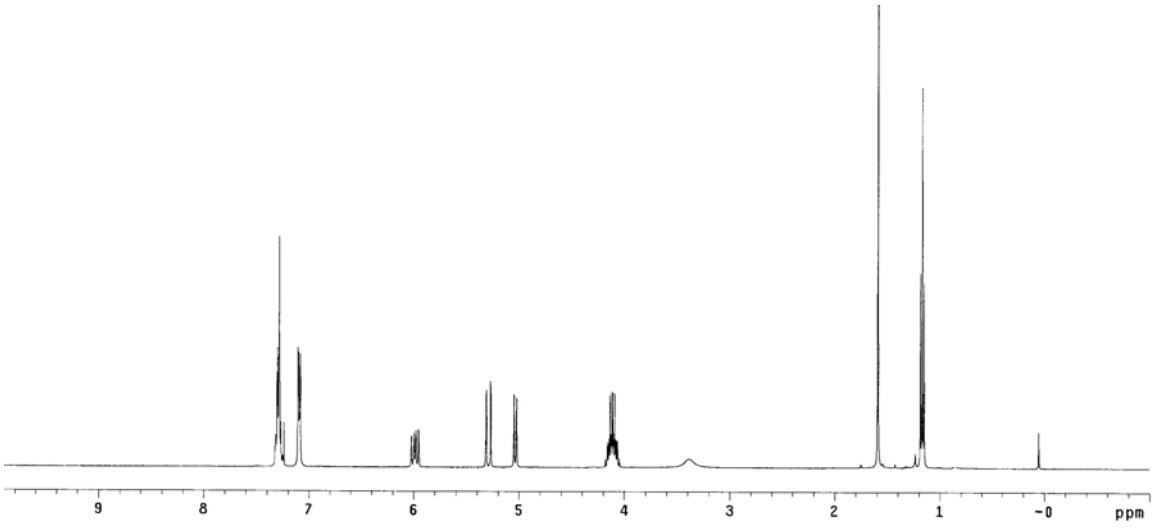
3.35

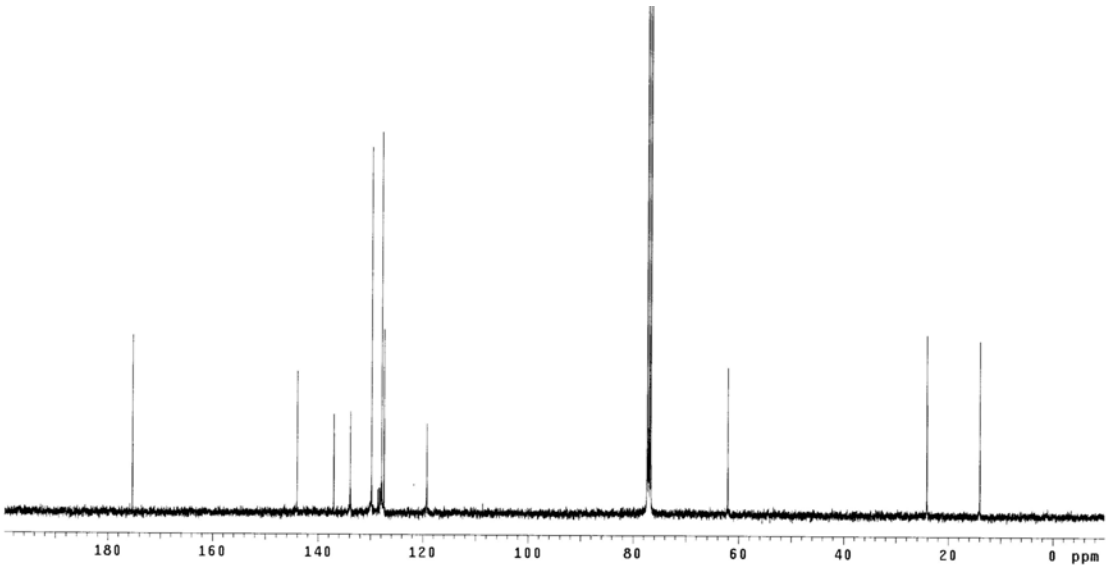


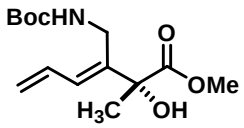




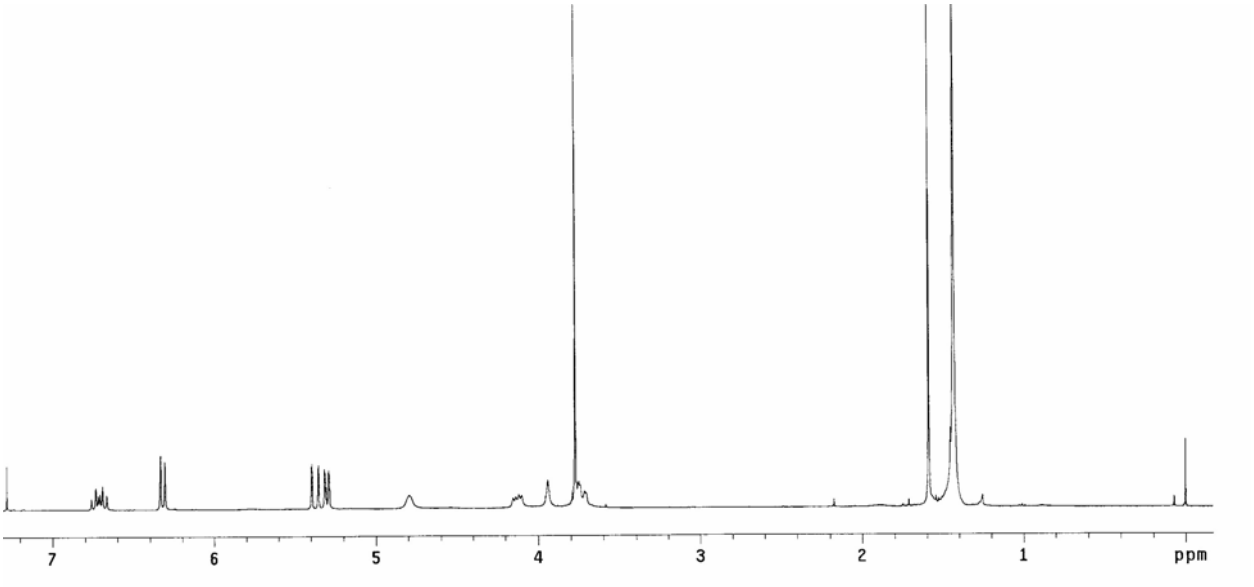
***deuterio*-3.35**






BocHN
O
OMe
H3C
OH

3.37


7
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5
4
3
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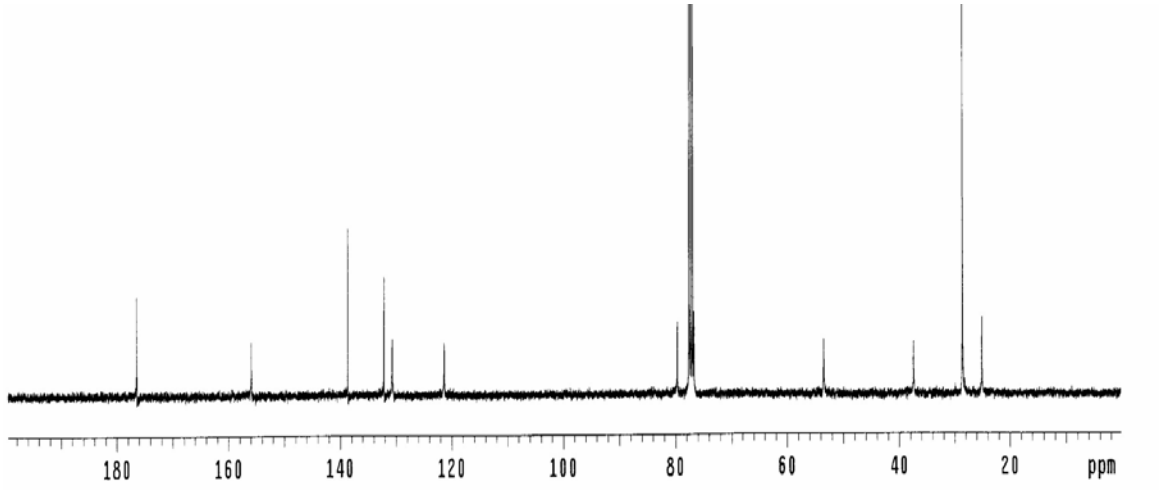
1
ppm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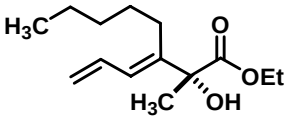
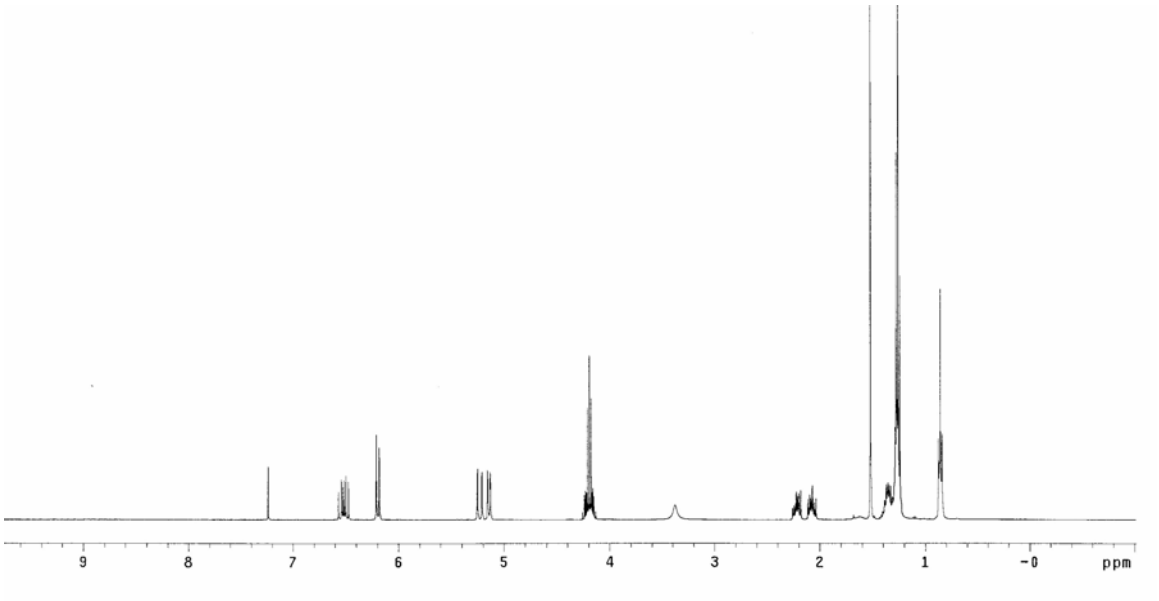
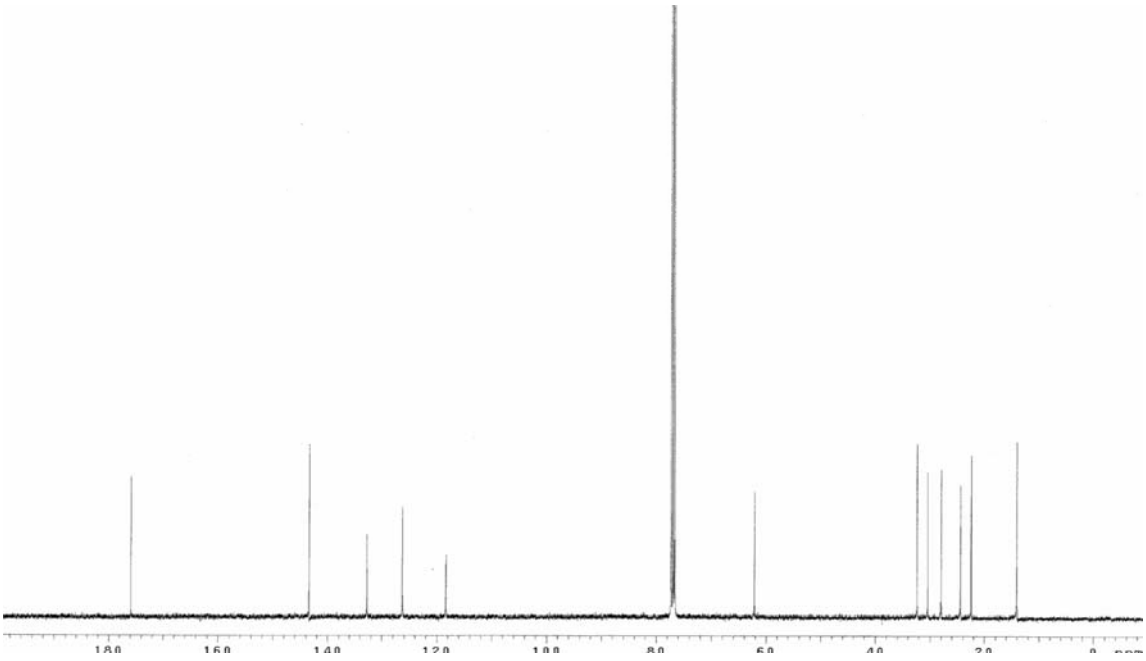
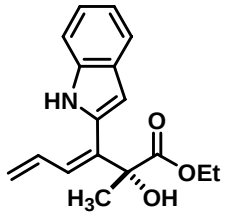
80
60
40
20
ppm



4.38



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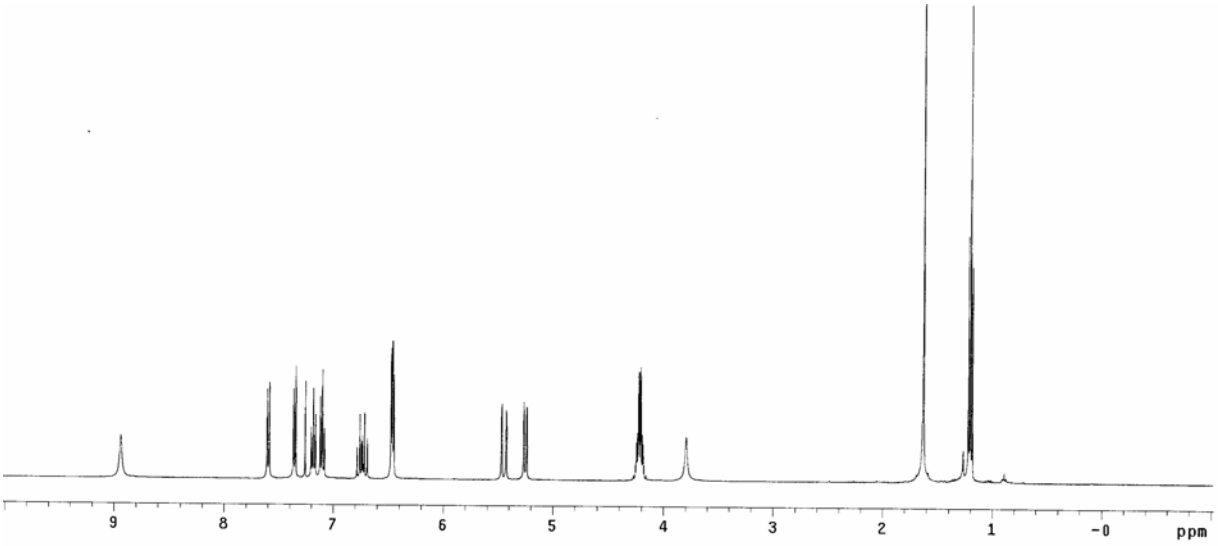
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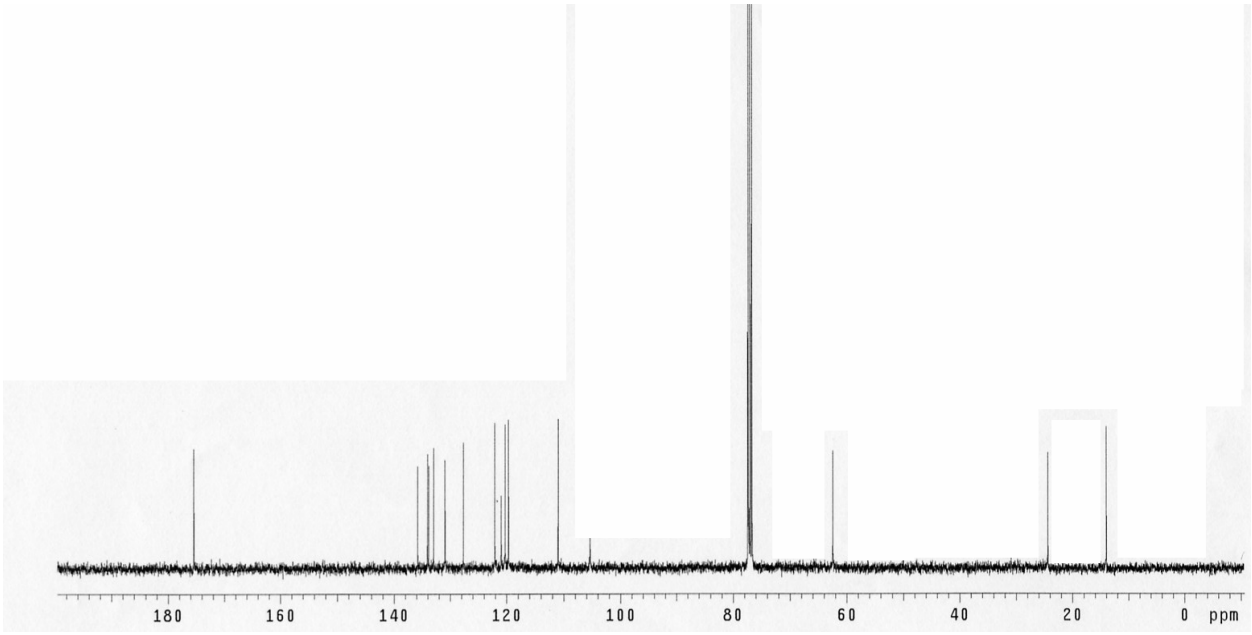
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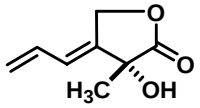

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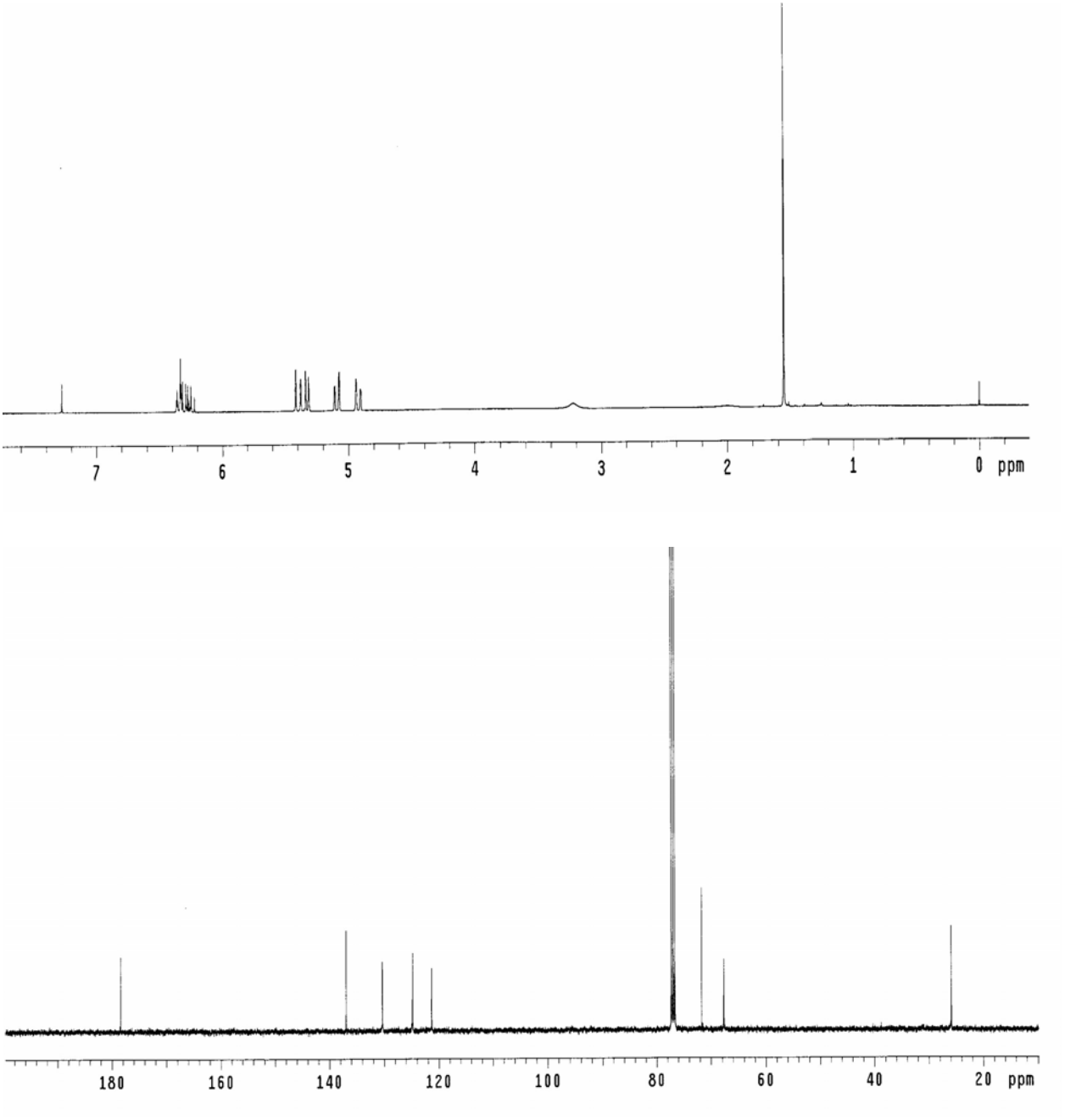

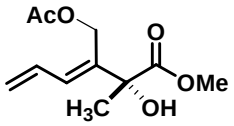

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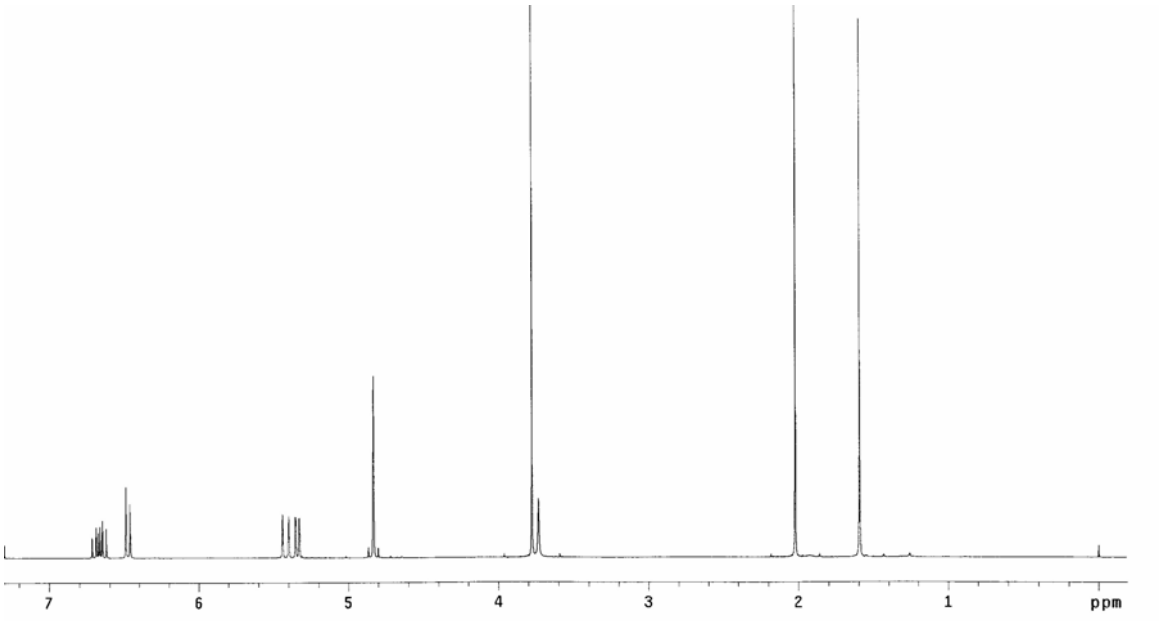

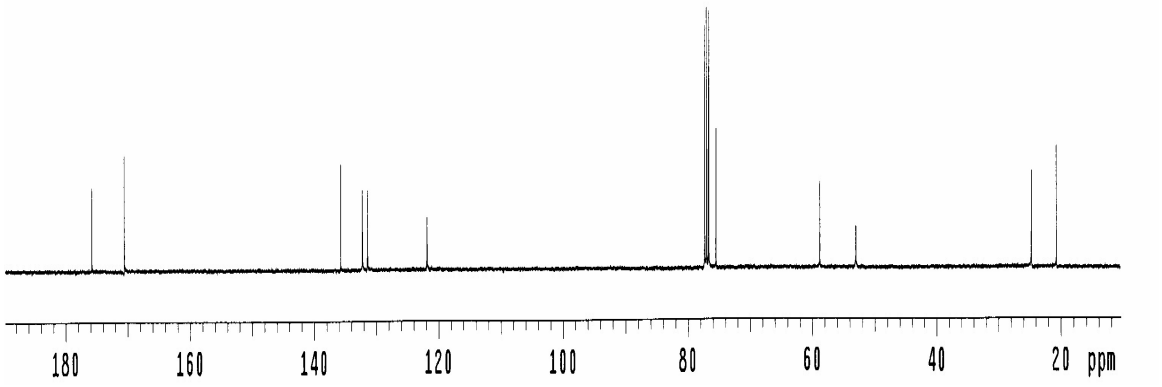

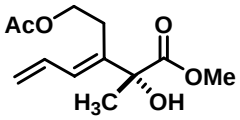

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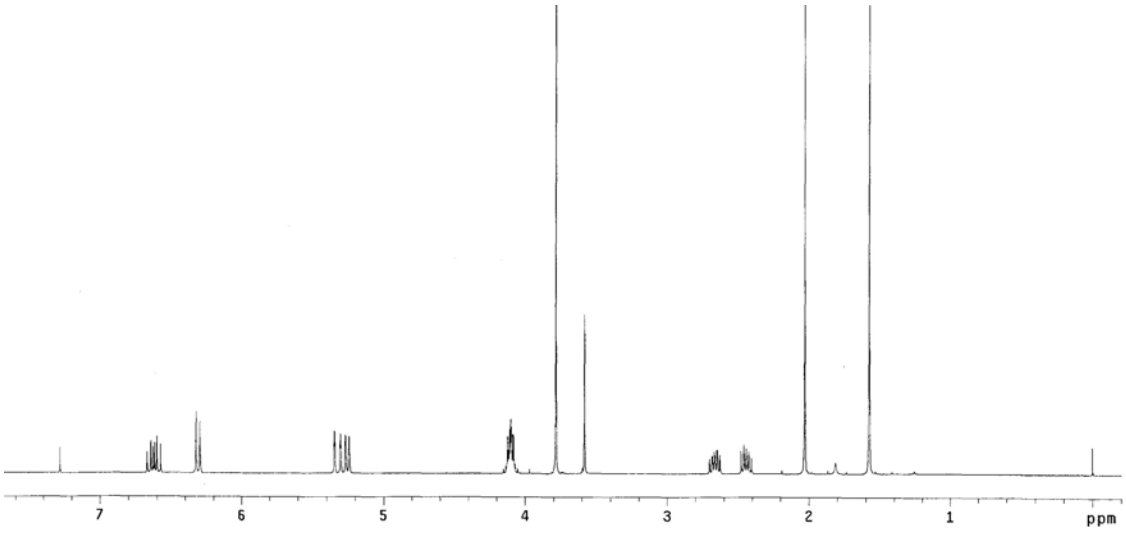

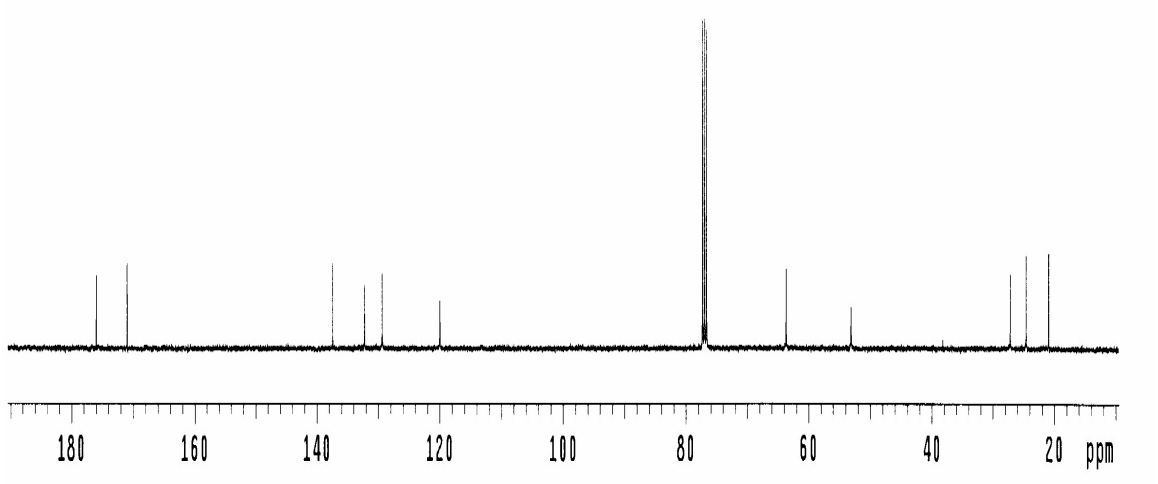

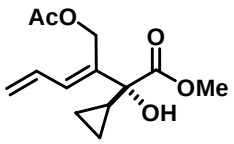

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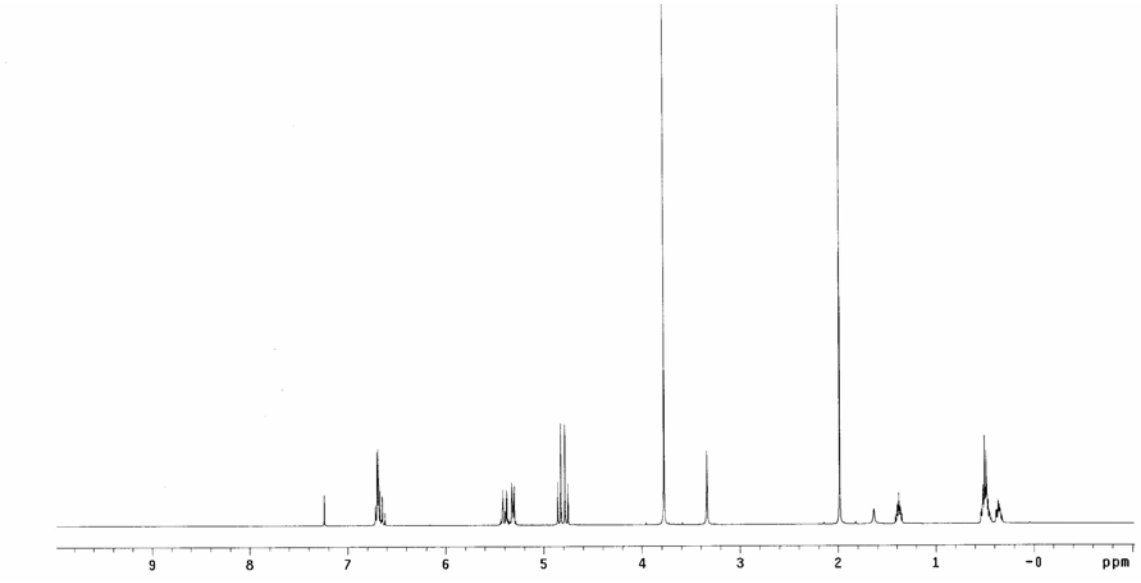

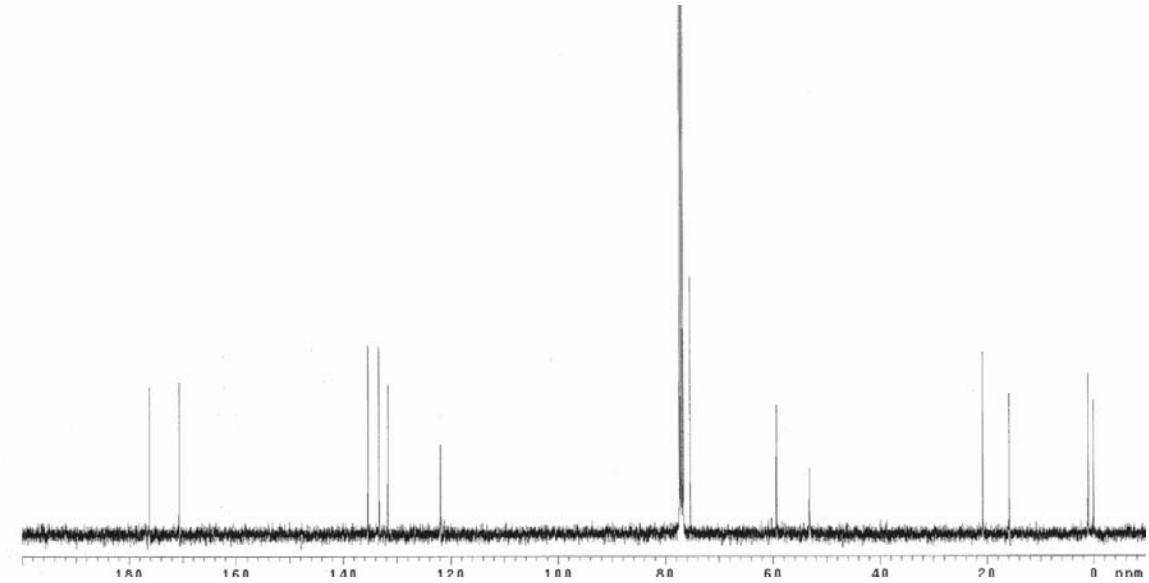

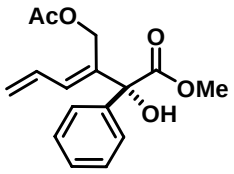

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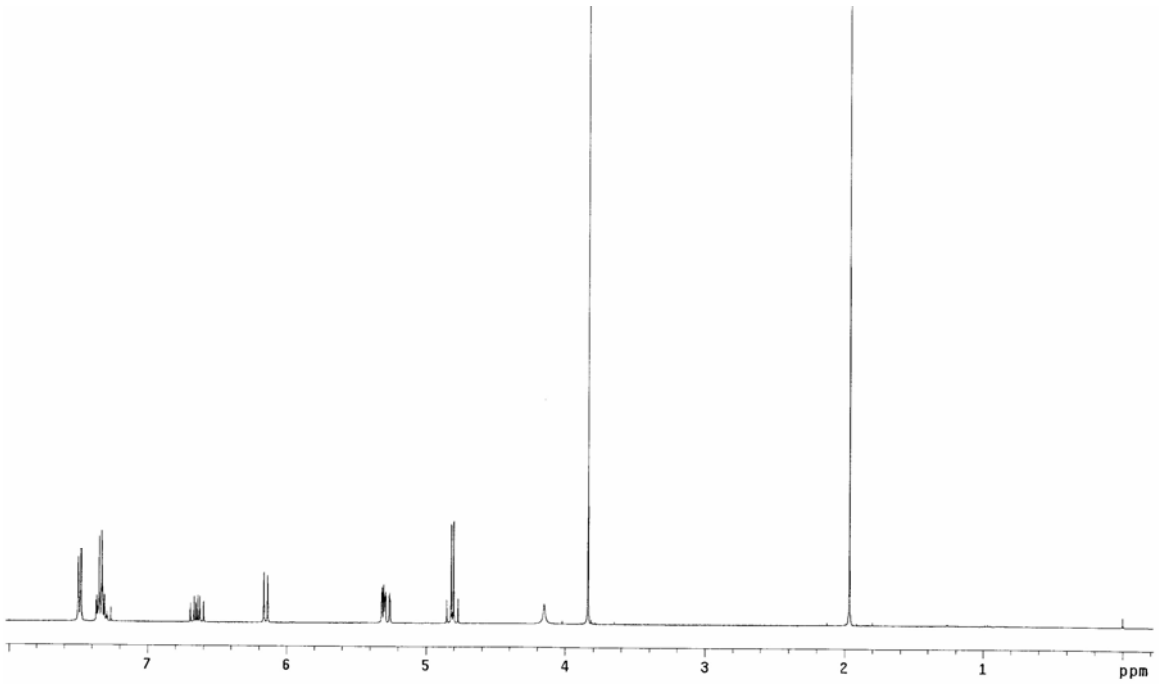

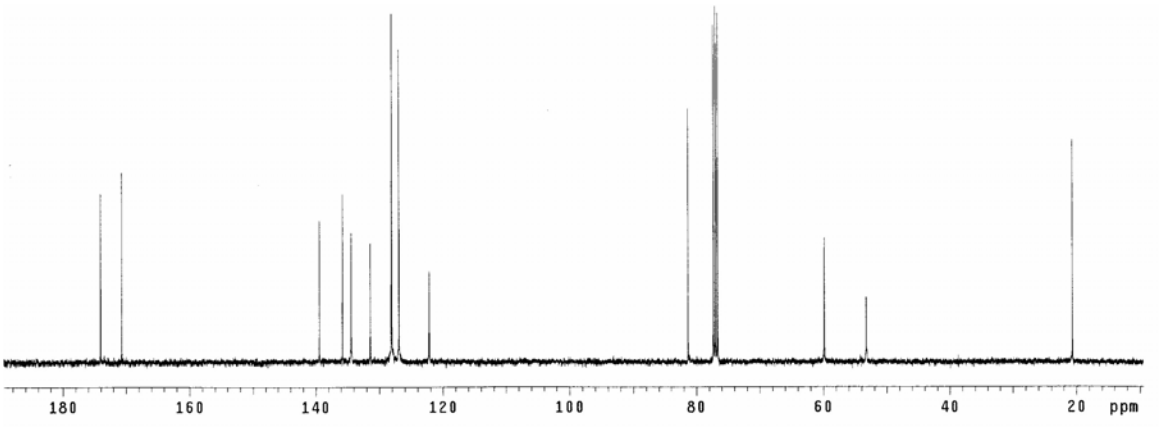

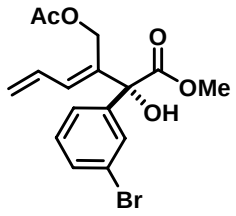

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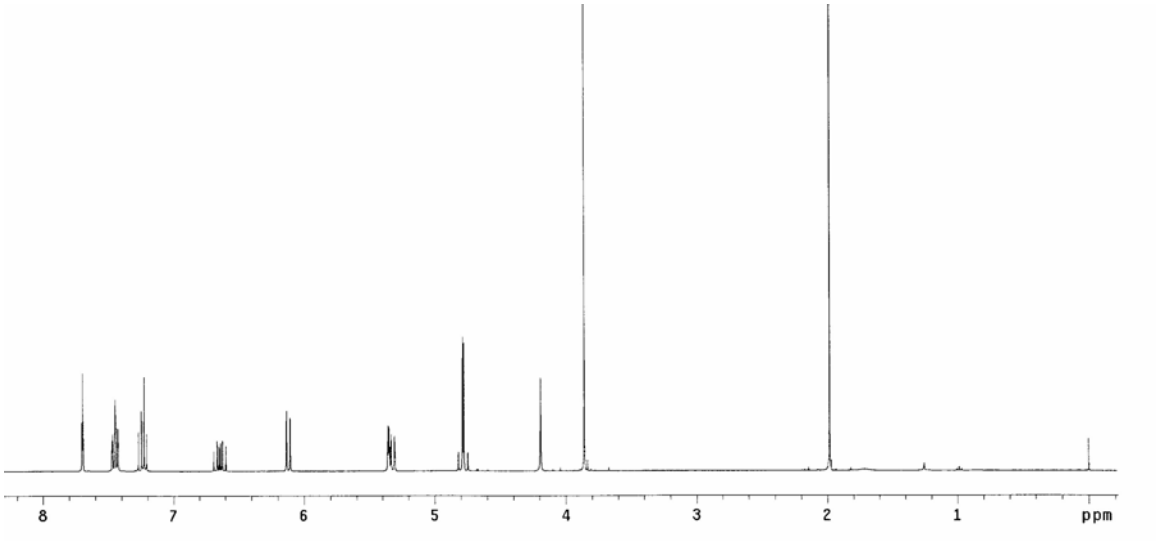

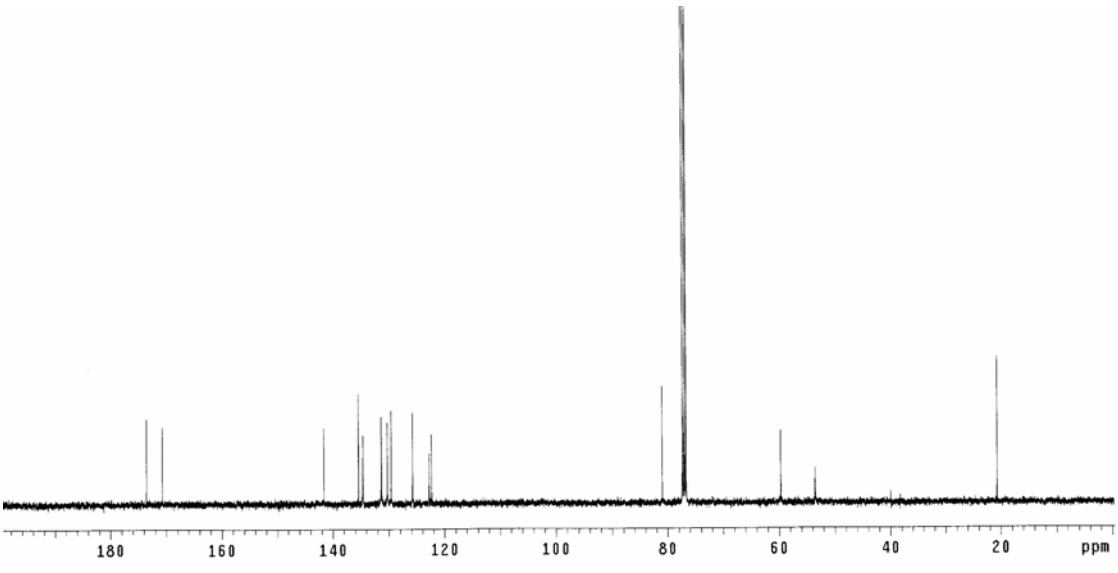

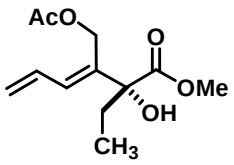
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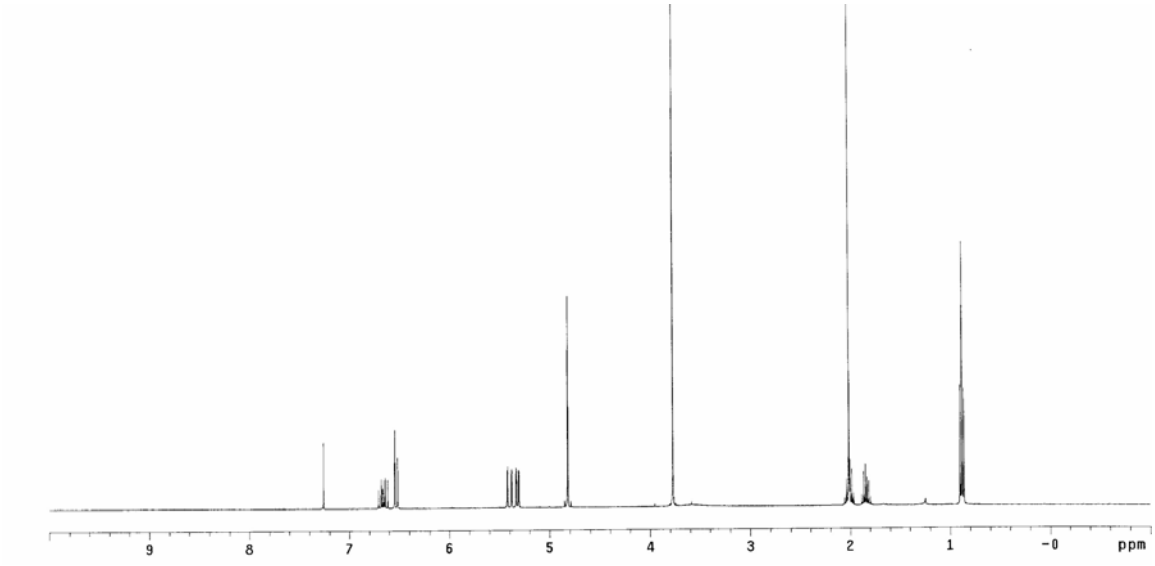
3.46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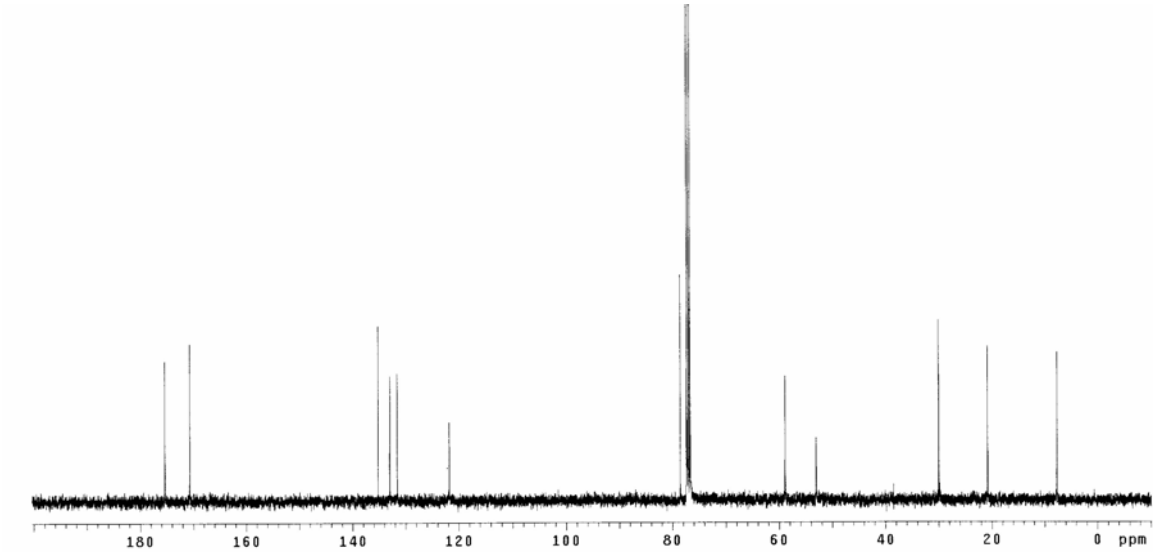
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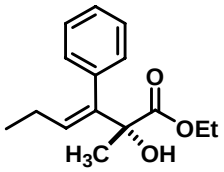

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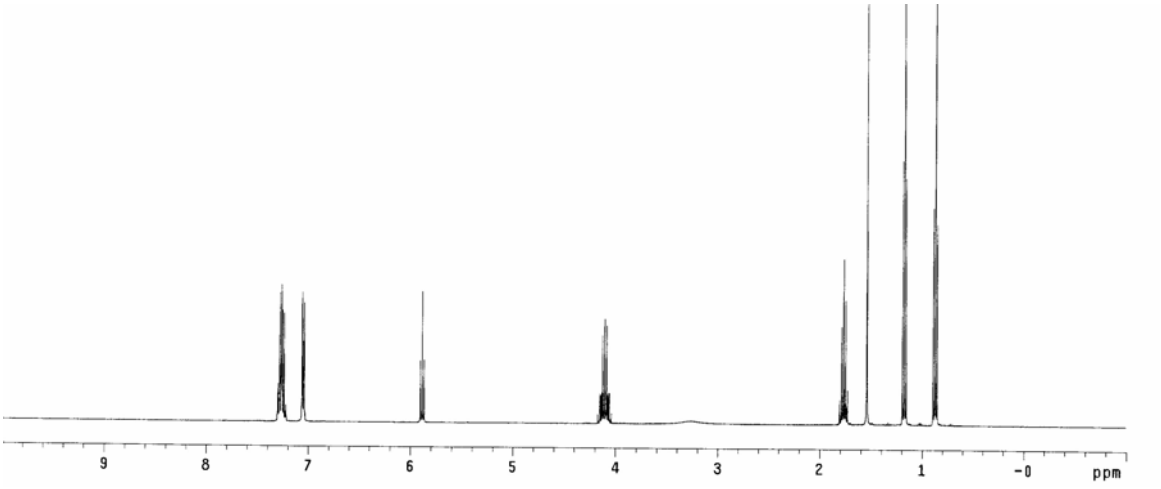

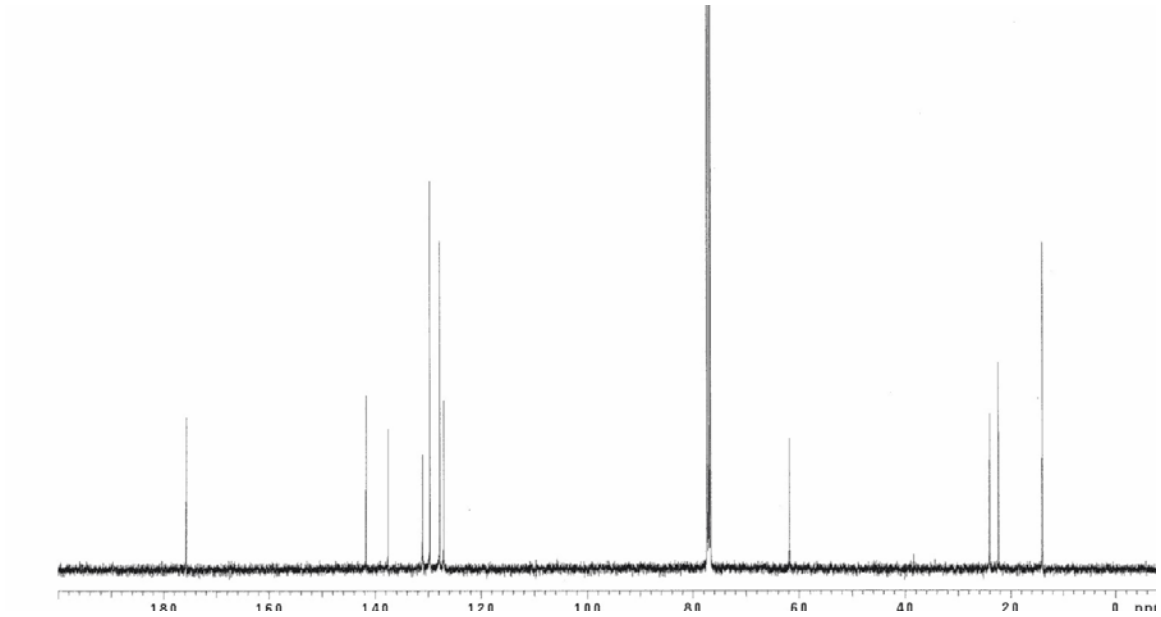

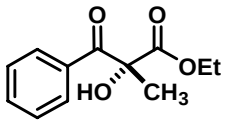
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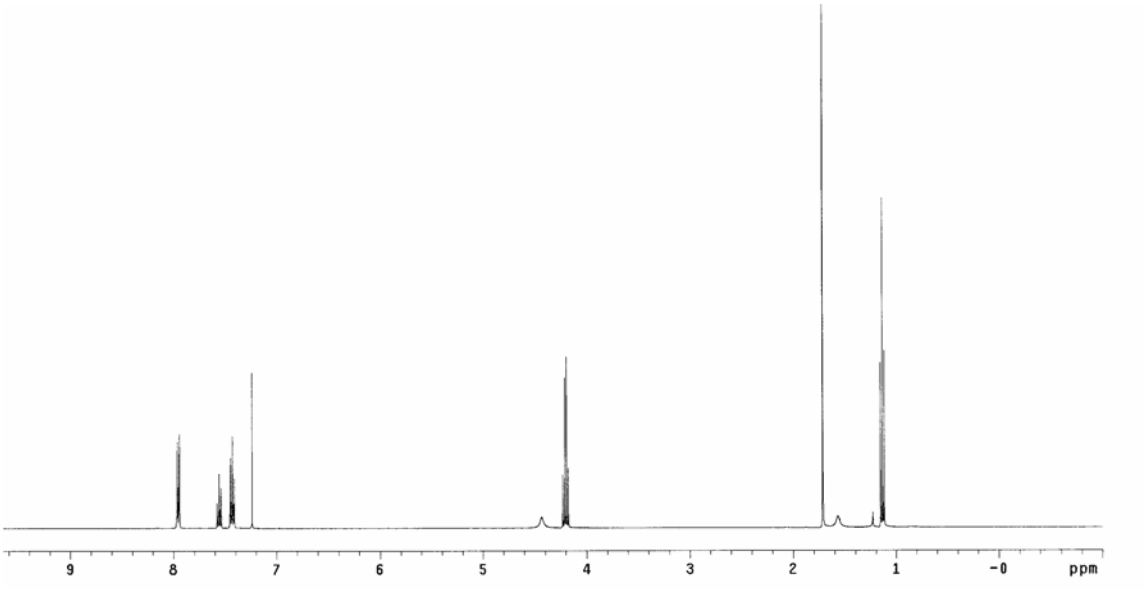
O
OEt
HO
CH3

6d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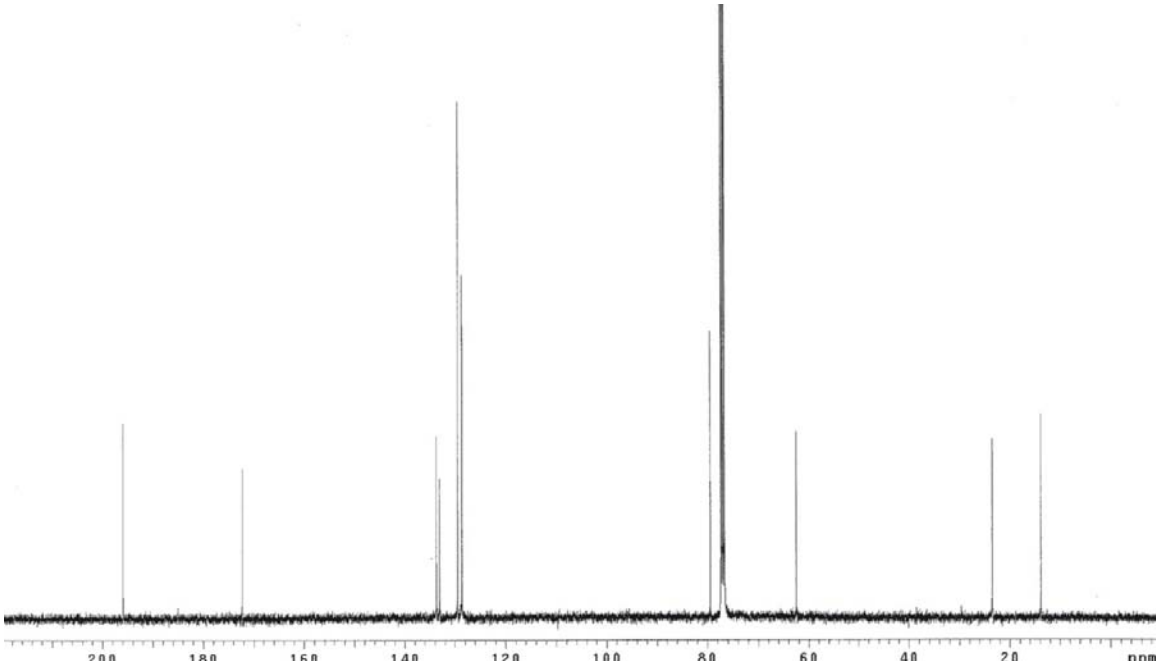
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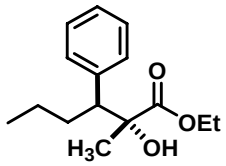
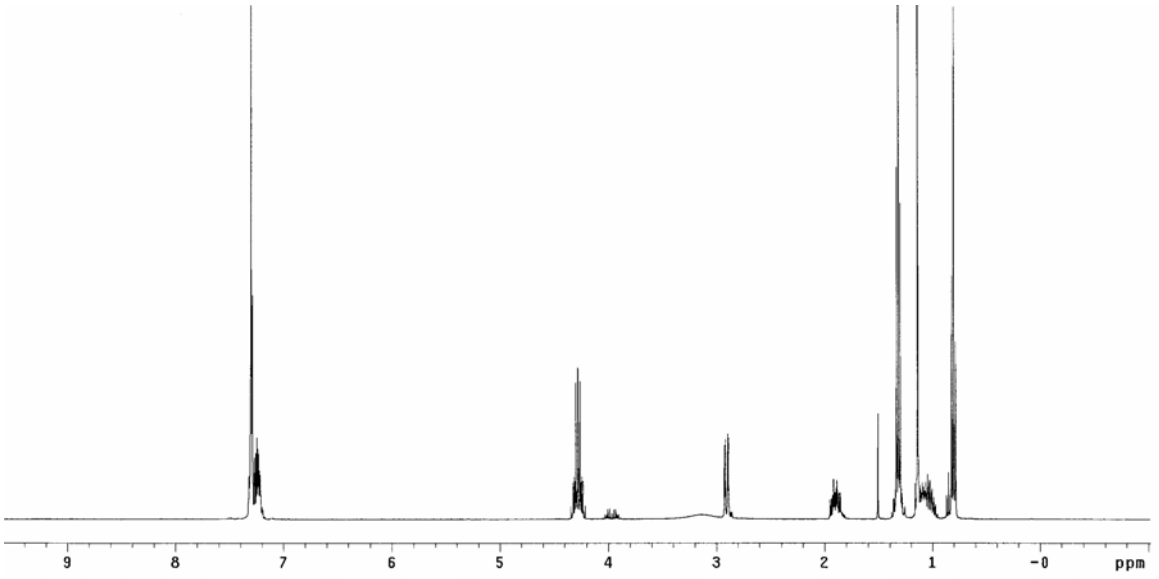
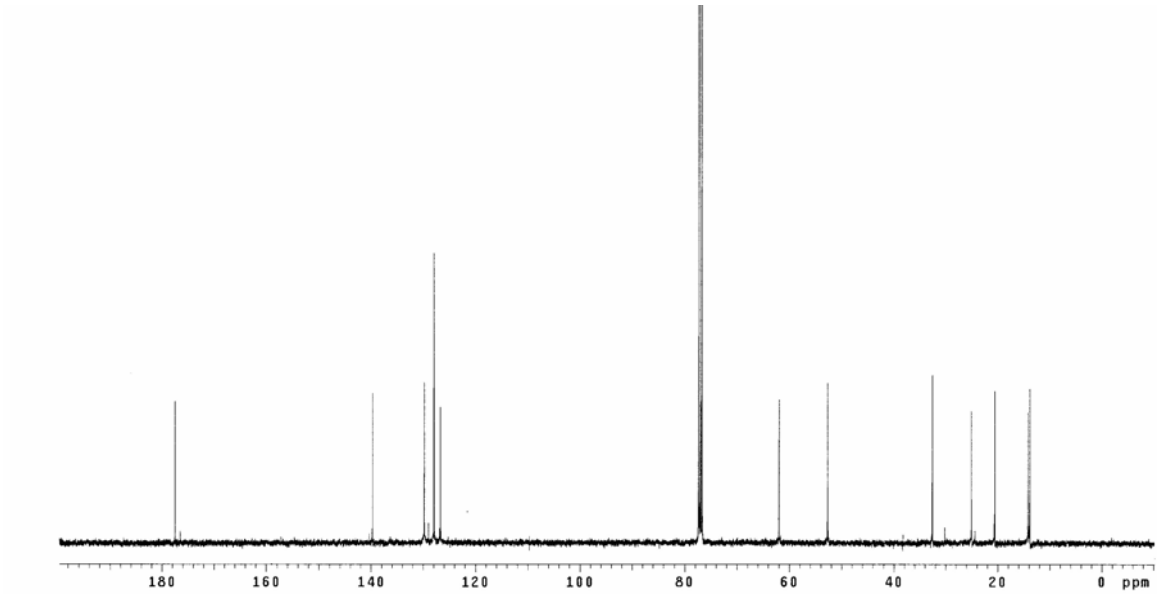
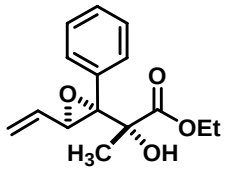


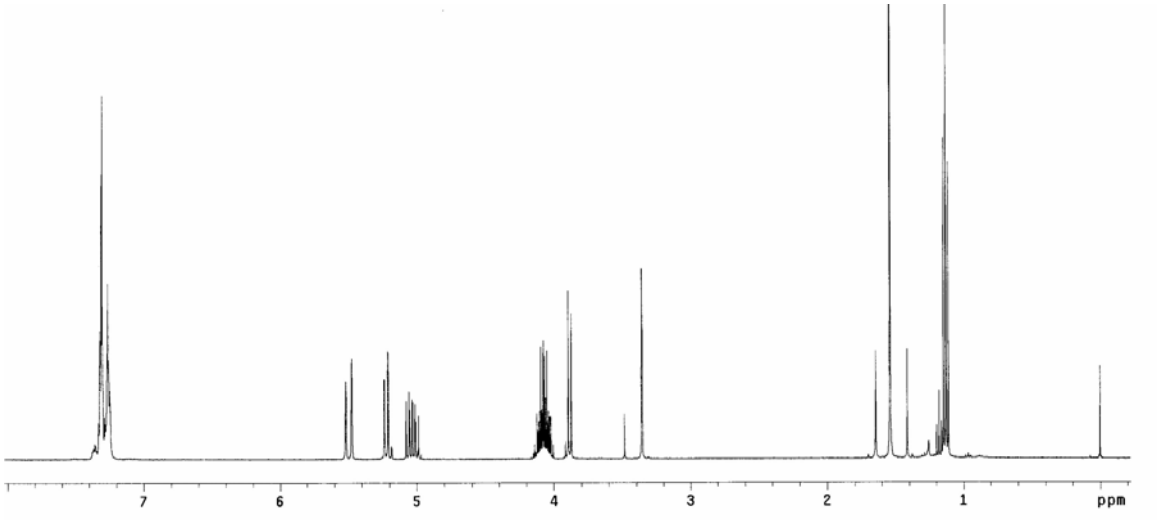
3.49
(mixture of two diastereomers)

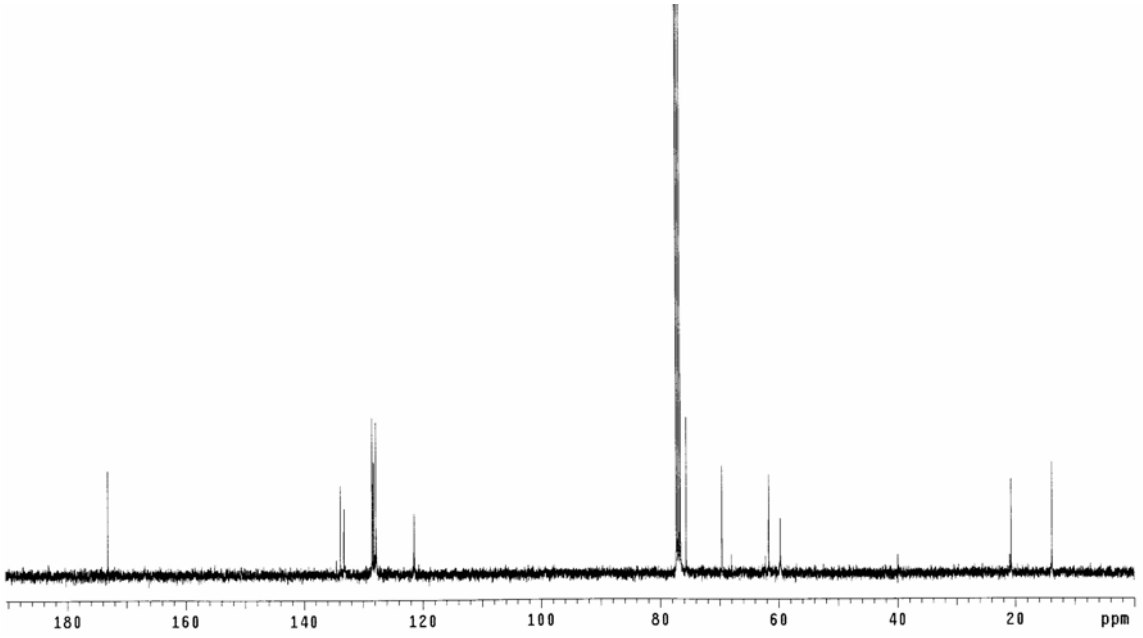


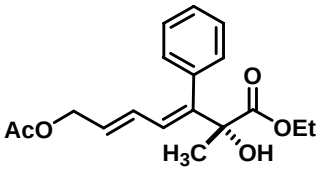




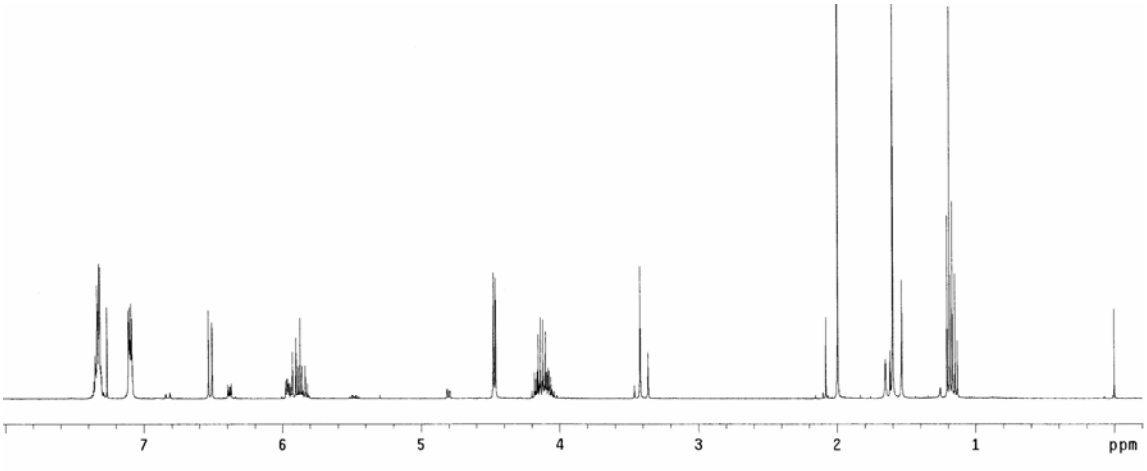
3.50
(mixture of two diastereomers)

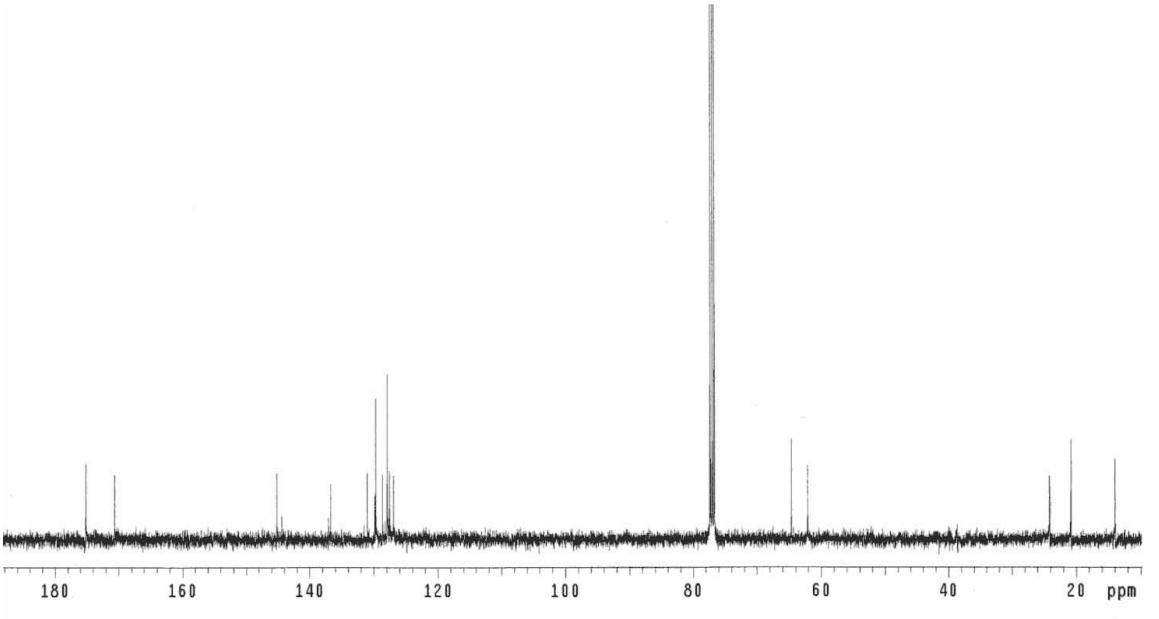


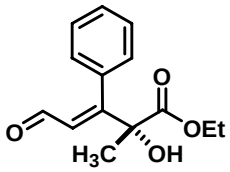




3.54
(mixture of two diastereomers)







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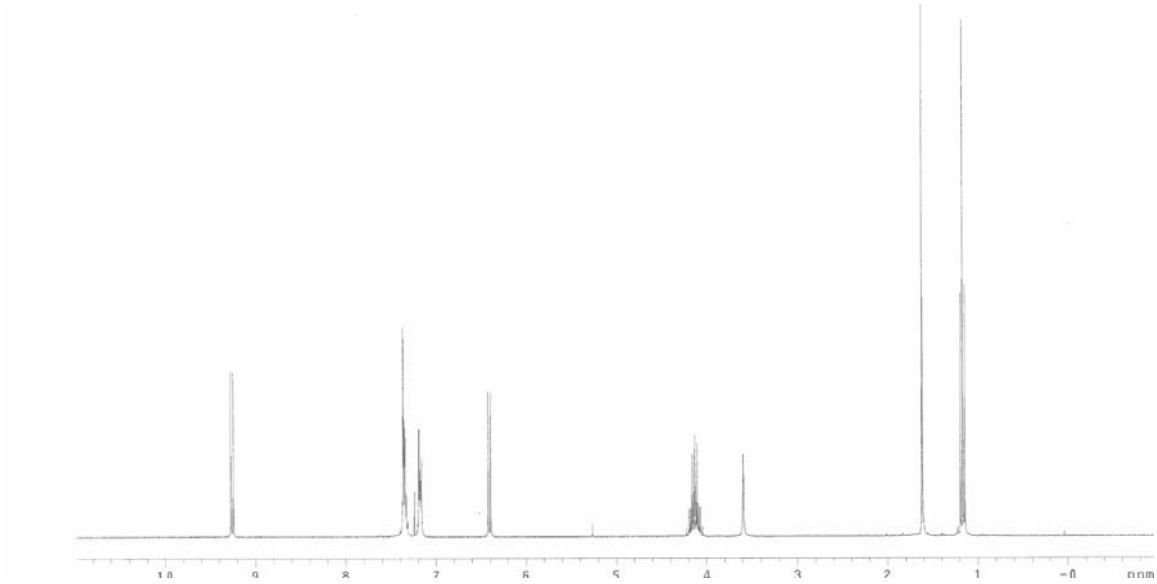

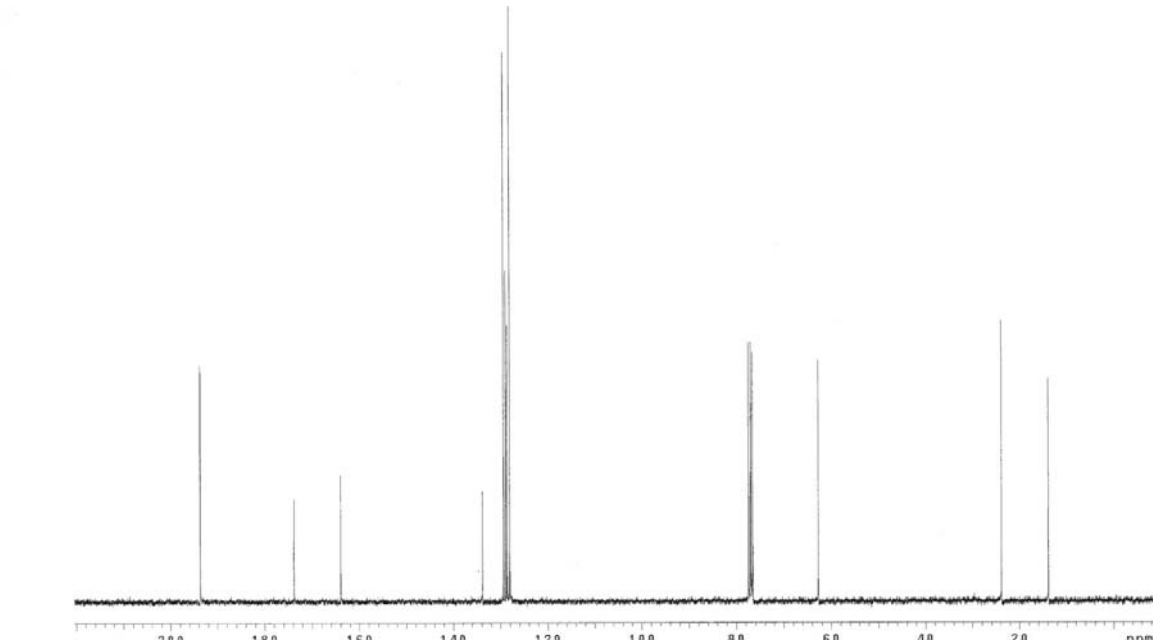

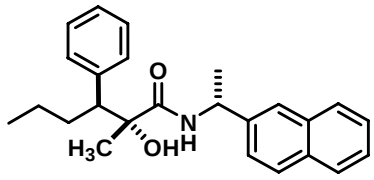

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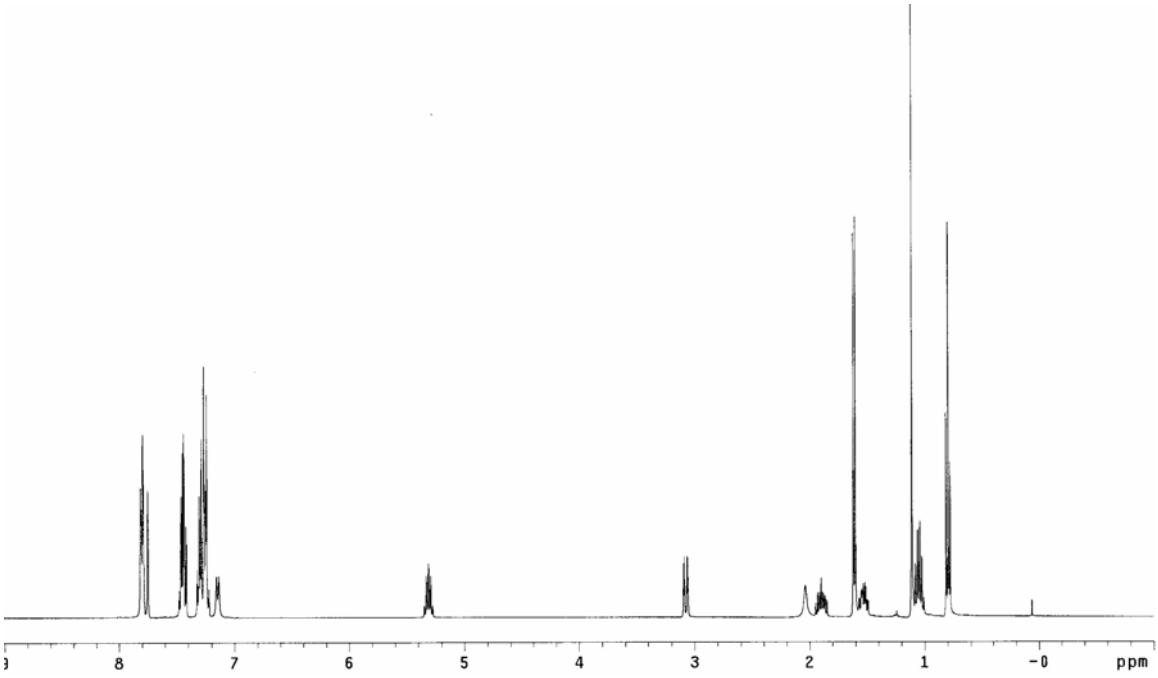

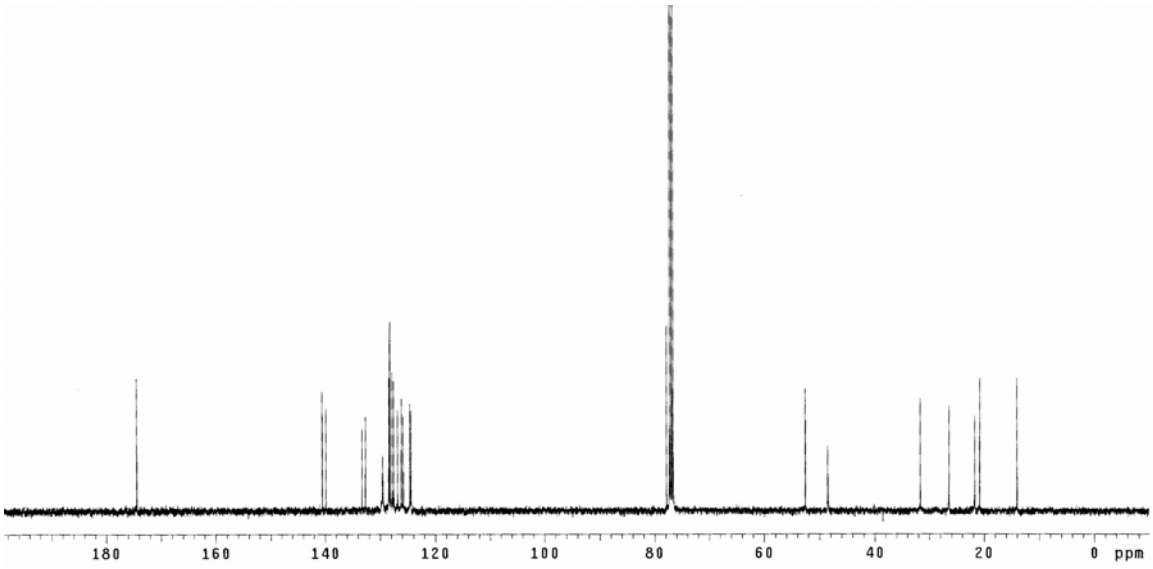

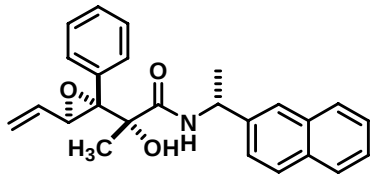

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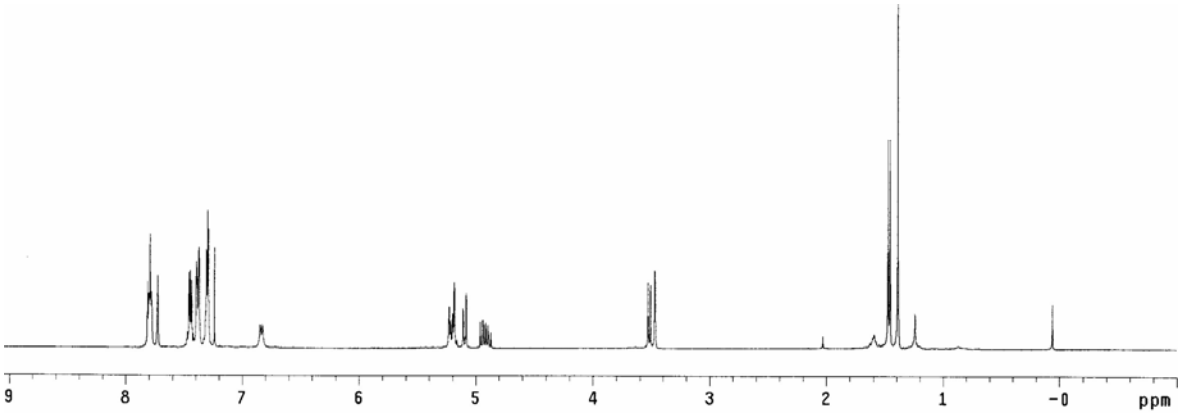

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[1] (a) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4074. (b) Huddleston, R. R.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 11488. (c) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 4664.

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[3] Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003.

[4] Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. J. *Am. Chem. Soc.* **1998**, *120*, 8011.

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[7] For σ-bond metathesis involving Rh(III) intermediates, see: (a) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, T.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc*. **2005**, *127*, 2538. (b) Liu, c.; Widenhoefer, R. A. *Organometallics* **2002**, *21*, 5666. (c) Hutschka, F.; Dedieu, A.; Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1742.

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Chapter 4 Multicomponent Reductive Coupling of Acetylene with Carbonyls and Imines

4.1 INTRODUCTION

Multicomponent reactions are generally defined as reactions in which more than two starting materials react, and essentially all atoms of the starting materials are incorporated into the product.[1] The goal of multicomponent processes is to achieve high levels of stuructural diversity by combining more than two simple and flexible building blocks in efficient one-pot protocols. Due to their inherent simple and concise experimental procedures, considerable attention has been devoted to the development of mutlicomponent reactions. In addition, hydrogen-mediated C-C bond formations[2] have attracted increasing attention owing to their atom economical[3] and environmentally friendly "green" benefits. Thus, multicomponent reductive coupling under hydrogenation conditions can be a powerful synthetic technology combining the advantages of multicomponent reactions and reductive coupling methods. In this section, we report three different types of hydrogen-mediated multicomponet reductive couplings: 1) multicomponent reductive coupling of acetylene and carbonyls, 2) multicomponent reductive coupling of acetylene and imines, and 3) multicomponent reductive coupling of acetylene and chiral aldehydes.

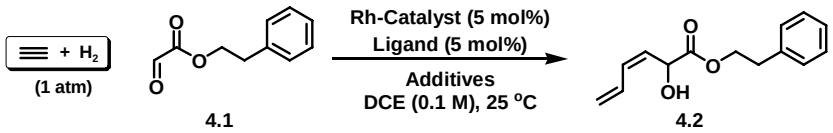
4.2 MULTICOMPONENT REDUCTIVE COUPLING OF ACETYLENE TO CARBONYLS

4.2.1 Optimization

To investigate the possibility of the multicomponent reductive coupling under hydrogenation conditions, we chose the reductive coupling of acetylene[4] and carbonyls as our model system. In this reductive coupling, four molecules are combined: two

molecules of acetylene, one molecule of a carbonyl compound, and elemental hydrogen to produce products of *Z*-dienylation.[5] Initial studies involved exposure of glyoxalate **4.1** to equal volumes of hydrogen and acetylene gas in the presence of $Rh(COD)_2OTf$(5 mol%) using triphenylacetic acid (TPAA, 5 mol%) as co-catalyst.[2d] Remarkably, the product of carbonyl *Z*-butadienylation **4.2** was formed in 32% yield (Table 4.1, entry 1). In the absence of the TPAA co-catalyst, compound **4.2** was formed in 17% yield (Table 4.1, entry 2). Though often overlooked, it is well documented that many catalytic processes involving charged organometallic complexes are dependent on the nature of the counterion.[6] We anticipated that the counterion would influence the Lewis acidity of our catalytic system. To test this hypothesis, we prepared rhodium complexes with varying couterion (OTf, BF_4, SbF_6, and "BARF" (BARF = $B(3,5\text{-}(CF_3)_2C_6H_3)_4$)). Indeed, with all other variables held constant, the counterion dramatically affected the reactivity. Precatalysts possessing chloride counter-ions provide none of the reductive coupling product. However, in the series $Rh(COD)_2X$, where the counter-ion X is OTf, BF_4, SbF_6 and BARF, counter-ions that coordinate less strongly than OTf uniformly provide **4.2** in higher yield (Table 4.1, entries 1, 4-6). This trend appears to reflect the increasing Lewis acidity of the metal center with weaker coordinating anions. Using $Rh(COD)_2SbF_6$ as precatalyst, some standard phosphine ligands were screened (Table 4.1, entries 5, 7-9). Best results were obtained using BIPHEP. Employing Na_2SO_4 as an additive, the yield of coupling product was increased to 59% (Table 4.1, entry 10). Presumably, Na_2SO_4 removes water, thus preventing the formation of catalytically inactive hydroxy-bridged rhodium dimers.[7] Finally, increasing the loading of TPAA (7.5 mol%) increased the yield of **4.2**, 68% (Table 4.1, entry 11).

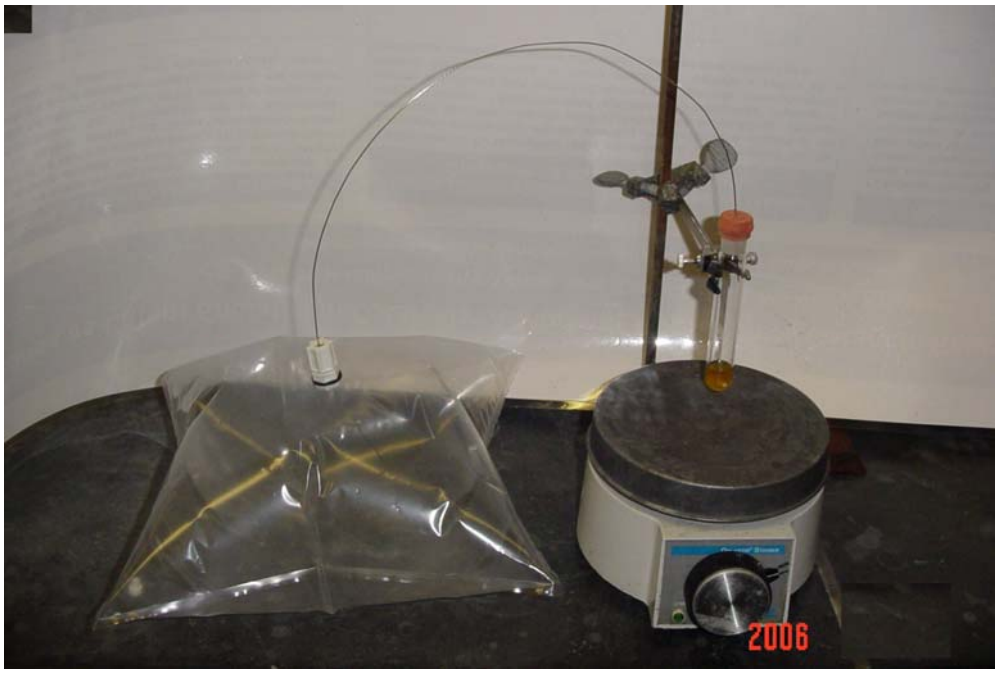
Table 4.1 Optimization table of multicomponent reductive coupling.



Entry	Rh-Catalyst	Ligand	Additive (mol%)	Additive (mol%)	Yield%
1	$Rh(cod)_2OTf$	BIPHEP	TPAA (5)	---	32
2	$Rh(cod)_2OTf$	BIPHEP	---	---	17
3	$[RhCl(cod)]_2$	BIPHEP	TPAA (5)	---	not observed
4	$Rh(cod)_2BF_4$	BIPHEP	TPAA (5)	---	41
5	$Rh(cod)_2SbF_6$	BIPHEP	TPAA (5)	---	51
6	$Rh(cod)_2BARF$	BIPHEP	TPAA (5)	---	52
7	$Rh(cod)_2SbF_6$	PPh_3	TPAA (5)	---	not observed
8	$Rh(cod)_2SbF_6$	DPPE	TPAA (5)	---	not observed
9	$Rh(cod)_2SbF_6$	*rac*-BINAP	TPAA (5)	---	29
10	$Rh(cod)_2SbF_6$	BIPHEP	TPAA (5)	Na_2SO_4 (200)	59
⇨ 11	$Rh(cod)_2SbF_6$	BIPHEP	TPAA (7.5)	Na_2SO_4 (200)	68

4.2.2 Importance of Apparatus

The mode of delivery of the two gases into the reaction mixture is crucial to the reaction's success. Though there is no kinetic data, we observed that stir-rate and reaction vessel surface area appear to affect the reaction rate. According to these observations, the reactions seem to be mass-transfer-limited with respect to introduction of hydrogen and/or acetylene gas.[8] Among the methods assayed, using an apparatus in which mixtures of hydrogen and acetylene are slowly delivered from a gas bag *via* cannula gave the best results (Figure 4.1)



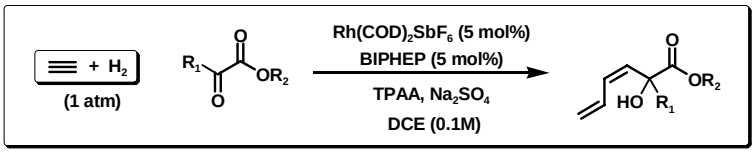
1) Reaction Vessel: 2.0cm (Diameter) * 13.0cm (Length)
2) Gas bag : Tedlar® gas sampling bag (Aldrich)
3) Cannula (Double-tipped needle): 24 in.(Length) – 20 (gauge)

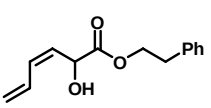
Figure 4.1 Apparatus for multicomponent coupling of acetylene and carbonyls.

4.2.3 Substrate Scope

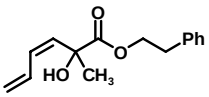
The optimized reaction conditions were successfully applied to a diverse set of carbonyl partners. In addition to glyoxate **4.1**, α-ketoesters were examined to expand the substrate scope. Phenethyl pyruvate also participated in this transformation to provide the desired product **4.3** in 73% yield. Sterically demanding cyclopropyl-oxo-acetic acid methyl ester underwent multicomponent reductive coupling to produce the corresponding product **4.4** in 55% yield. However, isopropyl-oxo-acetic acid ethyl ester did not afford the desired product. Additionally, a protected isatin underwent reductive coupling to furnish the desired product **4.5** in 81% yield. Finally, aryl-oxo-acetic acid ethyl esters were also exposed to the standard conditions to produce the corresponding products **4.6-4.8** in good yields (Table 4.2).

Table 4.2 Multicomponent coupling of acetylene with activated carbonyls.[9]

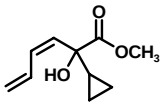




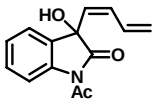
4.2 ,68% yield



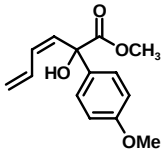
4.3, 73% yield



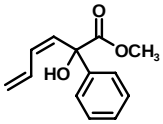
4.4, 55% yield



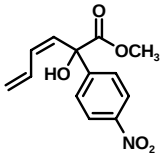
4.5, 81% yield



4.6, 57% yield



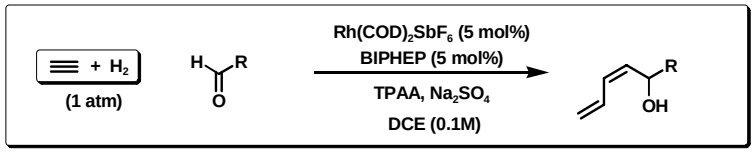
4.7, 77% yield

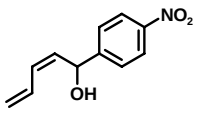


4.8, 88% yield

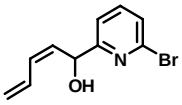
Notably, this multicomponent reductive coupling is applicable to simple (unactivated) aldehydes which have not yet been utilized in other hydrogenative reductive coupling methods reported by our group.[2] Gratifyingly, a variety of aldehydes participated in this reaction to afford the corresponding products **4.9**-**4.13a** in good yields (Table 4.3).

Table 4.3 Multicomponent reductive coupling of acetylene with aldehydes.

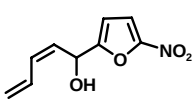




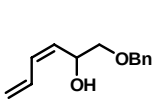
4.9, 63% yield



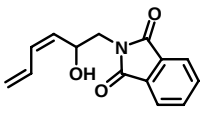
4.10, 56% yield



4.11, 72% yield

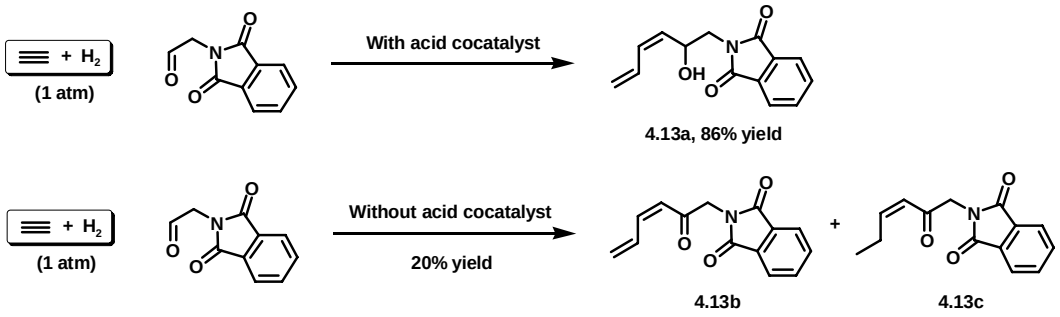


4.12a, 75% yield



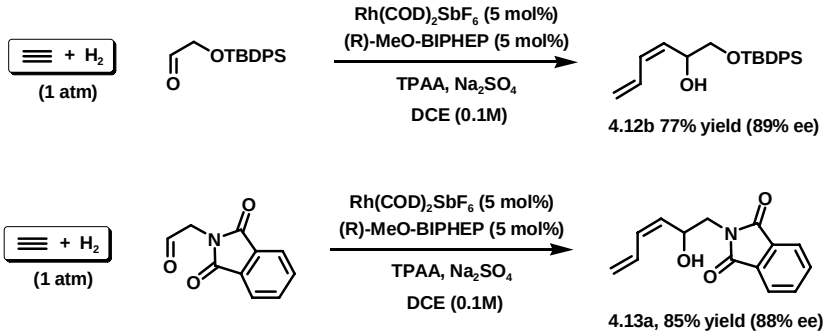
4.13a, 86% yield

However, this reductive coupling is still restricted to electron deficient aldehydes. Based on isolated yields and relative reaction rates, the reactivity of this reaction appears to be very sensitive to the electrophilicity of carbonyl coupling partners. Indeed, electron deficient carbonyls consistently gave better chemical yields than electron rich carbonyls. We speculate that the competitive reaction pathway, β-hydride elimination of a rhodium alkoxide intermediate, is favorable with electron rich carbonyl partners.[7,10] Interestingly, when the reaction was performed without Brønsted acid cocatalyst, this side reaction became a major pathway to produce the conjugated ketone **4.13b** along with terminally reduced conjugated ketone **4.13c** (Scheme 4.1).



Scheme 4.1 Critical role of acid cocatalyst.

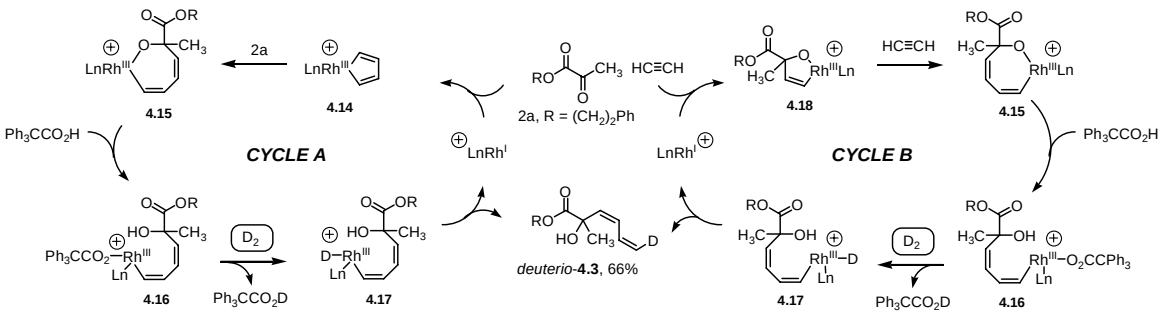
To further demonstrate the reaction scope, enantioselective *Z*-butadienylation was attempted on aldehydes. Gratifyingly, using a rhodium catalyst ligated by (R)-MeO-BIPHEP, the corresponding dienes **4.12b** and **4.13a** were produced in 88% and 89% ee, respectively (Scheme 4.2). Given the preliminary results of enantioselective reductive coupling of acetylene with aldehydes, the enantioselective reductive coupling of acetylene with α-ketoesters was tested. However, only moderate levels of enantio-seletivities with α-ketoesters were obtained.



Scheme 4.2 Enantioselective multicomponent coupling of acetylene and aldehydes.

4.2.4 Mechanistic Studies

To gain insight into the catalytic mechanism, the reductive coupling of acetylene gas and phenethyl pyruvate was conducted under a deuterium atmosphere. The product *deuterio*-**4.3** incorporated a single deuterium atom at the diene terminus as the *Z*-stereoisomer. We initially proposed two possible catalytic mechanisms (Scheme 4.3). In **Cycle A**, acetylene dimerization to form a rhodacyclopentadiene **4.14**[11,12] is followed by carbonyl insertion to furnish an oxarhodacycloheptadiene intermediate **4.15**. In **Cycle B**, the same oxarhodacycloheptadiene intermediate **4.15** is generated by acetylene-carbonyl oxidative coupling through intermediate **4.18** followed by insertion of a second acetylene molecule. Protonolytic cleavage of the rhodium-oxygen bond in the oxarhodacyclo-heptadiene **4.15,** followed by σ-bond metathesis[13] of intermediate **4.16** with elemental deuterium provides (alkenyldeuterido)-rhodium intermediate **4.17**, which upon C-D reductive elimination delivers *deuterio*-**4.3** and the starting rhodium(I) complex to close the cycle.



Scheme 4.3 Plausible catalytic mechanisms.

However, the deuterium labeling studies could not discriminate between **Cycle A** and **Cycle B**. In order to further probe the mechanisms, ESI studies were conducted. An aliquot of the crude reaction mixture from the hydrogen-mediated reductive coupling of gaseous acetylene to α-ketoester **4.19** was diluted 5000-fold in methanol, and directly subjected to ESI-mass spectroscopic analysis in the positive ionization mode. A representative ESI-mass spectrum of the reaction mixture sampled at one hour is shown in Figure 4.2. The most abundant ions, as assigned on the basis of their m/z values, correspond to species postulated to arise in **Cycle A**, as illustrated in Scheme 1. Of particular interest is the ion of m/z 677 which matches the molecular weight expected for the rhodacyclopentadiene **4.14** shown in **Cycle A** of Scheme 4.3. In addition, two other ions match the calculated molecular weights of the oxarhodacycloheptadiene (m/z 900) and the following product of protonolytic cleavage by triphenylacetic acid (m/z 1188). In contrast, ions corresponding to the oxarhodacyclopentadiene species **4.18** (calculated molecular weight 874 Da) of **Cycle B** are not observed.

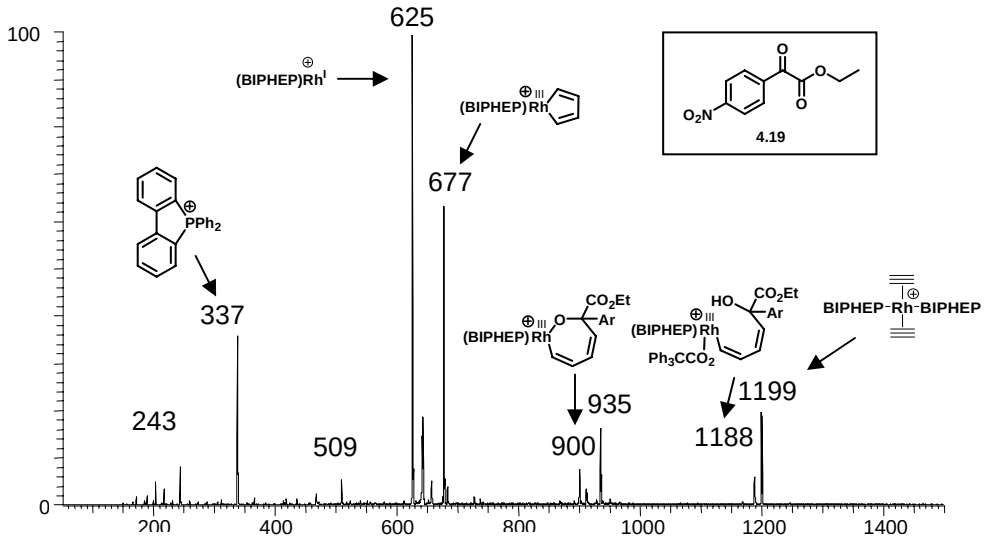


Figure 4.2 ESI Mass full scan spectrum for the reductive coupling of acetylene to α-ketoester.

The structural assignment of the ion of m/z 1188 is corroborated by multi-stage collisional activated dissociation (CAD) (Figure 4.3). This ion dissociates by loss of 288 Da, consistent with the elimination of triphenylacetic acid to regenerate the oxarhodacycloheptadiene intermediate **4.15** (m/z 900). When the latter intermediate is subjected to a second stage of CAD, it dissociates to an ion of m/z 677 which again matches the molecular weight of the rhodacyclopentadiene species shown in **Cycle A**, suggestive of a retro carbonyl insertion process. This ESI-MS data offers support for catalytic **Cycle A**, as shown in Scheme 4.3, but does not offer any evidence in support of catalytic **Cycle B**.

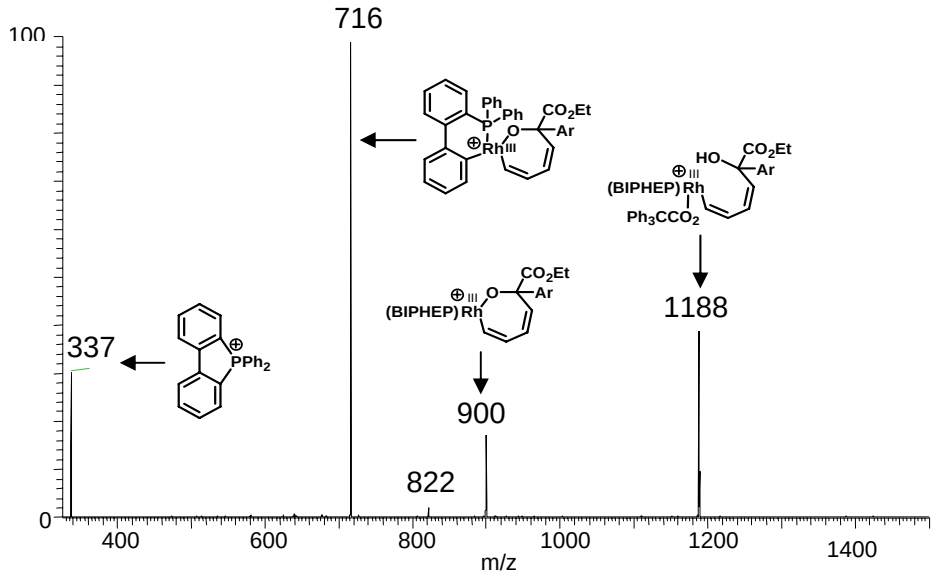


Figure 4.3 MS/MS spectrum of m/z 1188.

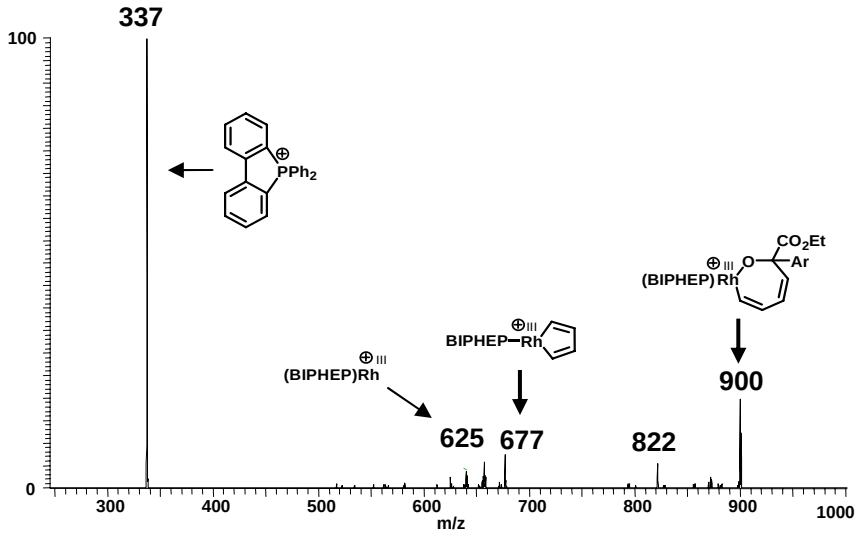
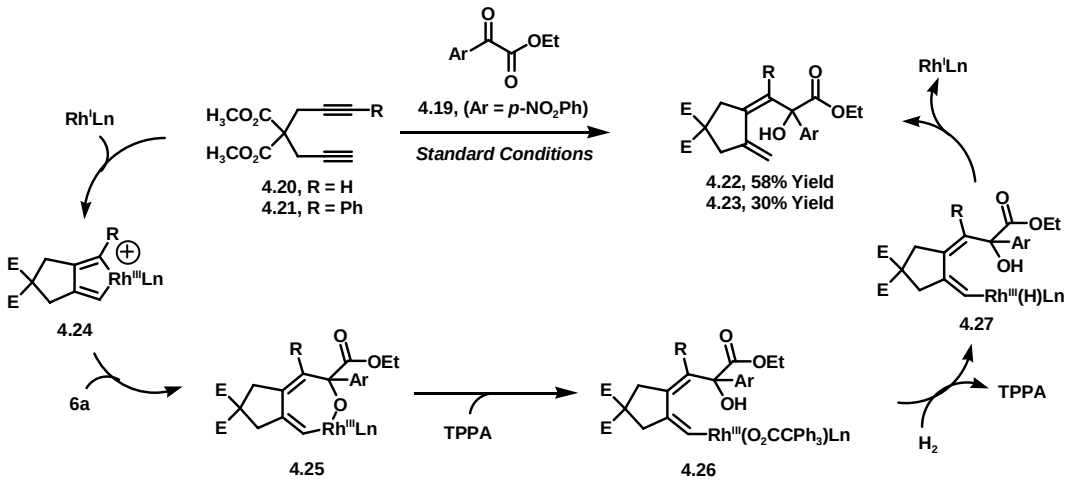


Figure 4.4 MS/MS/MS Spectrum of m/z 900.

4.2.5 Extension to Intramolecular Multicomponent Reductive Coupling

If catalytic **cycle A** is operative, one would expect related rhodacyclopentadiene species to exhibit similar reactivity and engage in carbonyl insertion processes. 1,6-Diynes are known to react with rhodium(I) salts to afford crystalline rhodacyclopentadienes,[10] which have been fully characterized. Accordingly, 1,6-diyne **4.20** (100 mol%) was hydrogenated in the presence of α-ketoester **4.19** (100 mol%). The product of tandem reductive cyclization[14] carbonyl coupling **4.22** was obtained in 58% yield as a single alkene geometrical isomer. Thus, as anticipated, the rhodacyclopentadiene intermediate **4.24** presumed to arise through oxidative coupling of the 1,6-diyne exhibits reactivity akin to that observed for the parent rhodacyclopentadiene obtained in couplings of gaseous acetylene. For nonsymmetric 1,6-diyne **4.21**, tandem reductive cyclization-carbonyl insertion occurred such that α-ketoester **4.19** coupled at the substituted terminus of the rhodacyclopentadiene intermediate **4.24** to furnish **4.23** through intermediates **4.45-4.27** as a single geometrical and constitutional isomer. The relatively modest yields of tandem reductive cyclization-carbonyl insertion products **4.22** and **4.23** are due to competitive alkyne [2+2+2] cycloaddition[15] (Scheme 4.4).



Scheme 4.4 Reductive coupling of 1,6-diynes with α-ketoester **4.19**.

In order to further support the proposed catalytic mechanism, ESI studies were conducted for this reaction. As expected, the ion of m/z 909 matches the molecular weight expected for the rhodacyclopentadiene **4.24** shown in Scheme 4.3. In addition, the other ion matches the calculated molecular weights of the oxarhodacycloheptadiene **4.25** (m/z 1132). However, in this ESI study, the ion corresponding molecular weight expected for the intermediate **4.26** was not detected (Figure 4.4).

The structural assignment of the ion of m/z 1132 is corroborated by multi-stage collisional activated dissociation (CAD) (Figure 4.5). This ion dissociates by loss of 223 Da, consistent with the elimination of α-ketoester **4.19** to regenerate the oxarhodacycloheptadiene intermediate **4.24** (m/z 909) and rhodium BIPHEP complex (m/z 625). The results of these ESI studies are consistent with our proposed catalytic mechanism (Figure 4.6).

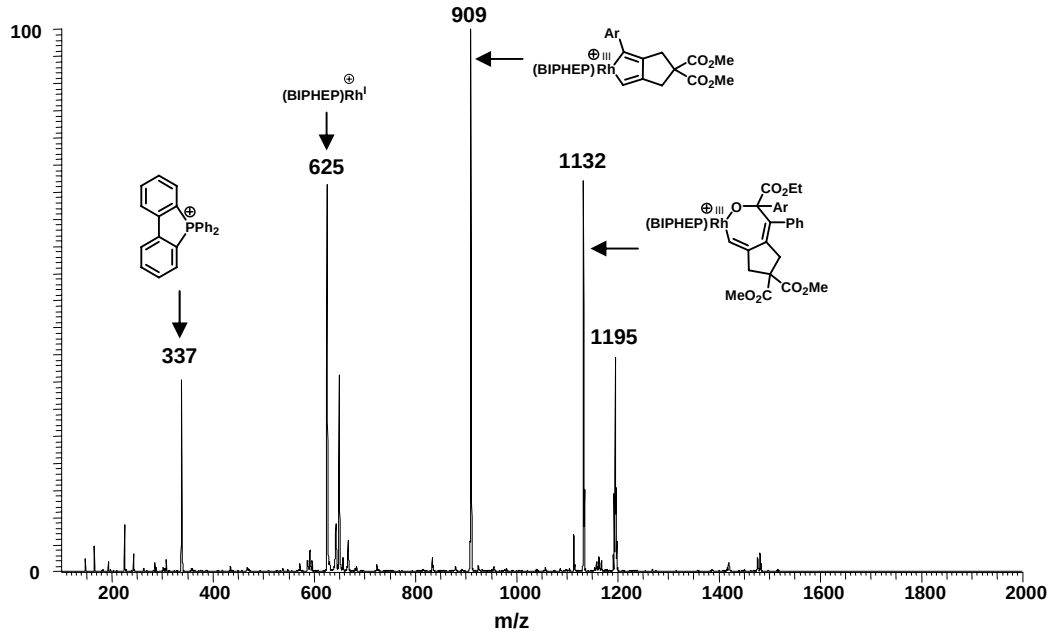


Figure 4.5 ESI Mass full scan spectrum for the reductive coupling of 1,6-diyne to α-ketoester.

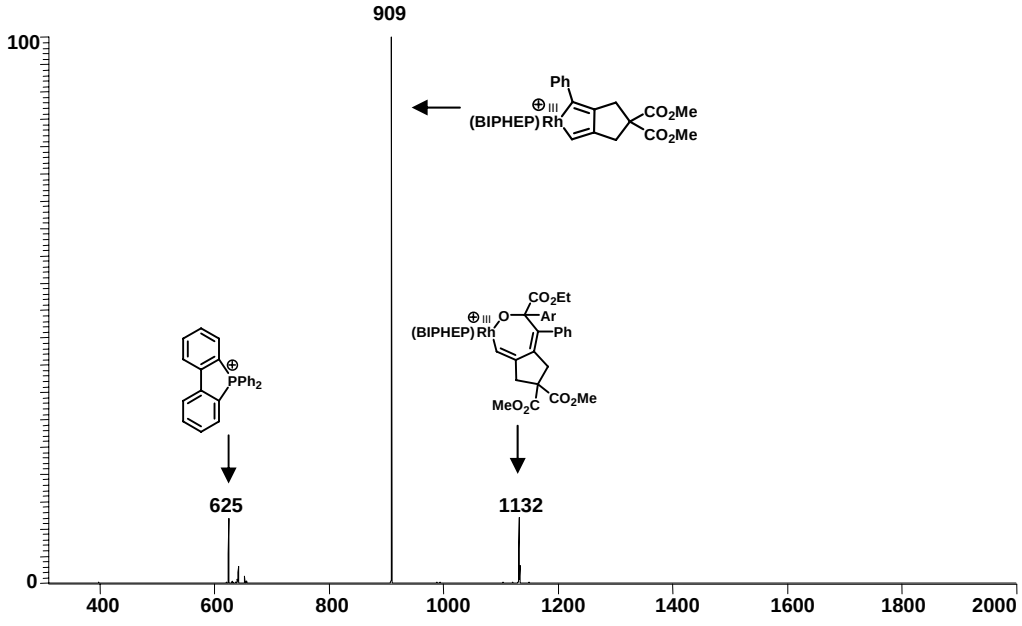


Figure 4.6 MS/MS spectrum of m/z 1132.

4.3 MULTICOMPONENT REDUCTIVE COUPLING OF ACETYLENE TO IMINES

4.3.1 Introduction

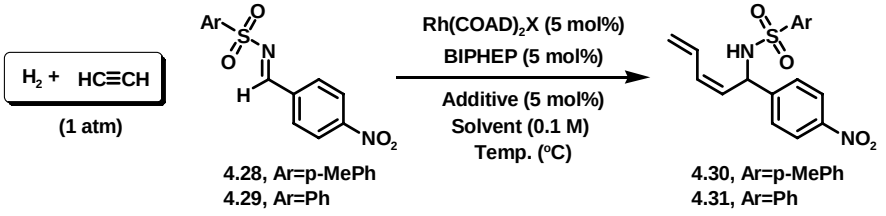
Enantiomerically enriched allylic amines are frequently used as synthetic intermediates, auxiliaries, and resolving agents in the synthesis of both natural and unnatural products.[16] Accordingly, there are many effective methods to access allylic amines.[17,18] However, most methods for catalytic enantioselective coupling of nonstabilized carbanion equivalents to imines rely upon preformed organometallics. Further, many organometallics used in such transformations are prepared via transmetallation. Here, preparation of the "primary organometallic" may itself require preexisting functionality to direct regiocontrolled metallation. For example, in metal-catalyzed imine arylations employing organoboron reagents,[19] aryllithiums that are prepared via metal-halogen exchange using *n*-BuLi are then transmetallated to boron. Here, three metallic reagents are used stoichiometrically prior to C-C coupling! Direct methods for the catalytic asymmetric coupling of nonstabilized organic fragments to imines circumvent use of preformed organometallics. Given the success in the multicomponent reductive coupling of acetylene with carbonyls,[9] the asymmetric muticomponent reductive coupling of acetylene with imines was explored as a means of accessing enantiomerically enriched allylic amines.

4.3.2 Optimization

Initial studies involved exposure of *N*-(*p*-toluenesulfonyl) aldimine **4.28** to ambient pressure of acetylene and hydrogen gas at ambient temperature using conditions developed for the related aldehyde couplings as the starting point for optimization. Under aforementioned conditions, the desired product **4.30** was obtained in 8% yield. Then the

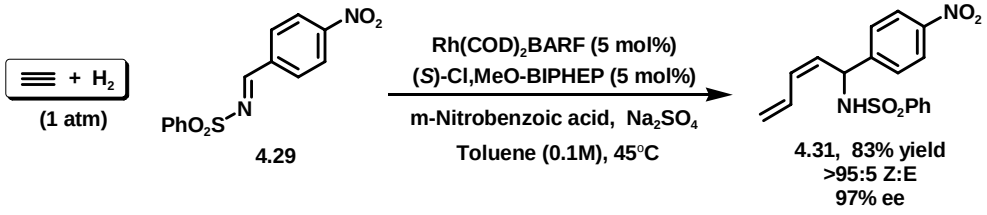
use of [Rh(COD)$_2$]BARF as precatalyst provided **4.30** in higher yield. By increasing reaction temperature to 40 ^{o}C, the yield of coupling product **4.30** was increased to 21% yield. At this point, we decided to screen reaction media. Among solvents assayed, toluene gave a higher yield at an elevated temperature. To further optimize the chemical yield, a systematic assay of Brønsted acids was performed. Among acids assayed, *m*-nitrobenzoic acid was identified as the optimal cocatalytst to provide the desired product in 68% yield. During the process of optimization, we observed that the color of the reaction media turned to the black at 80 ^{o}C. This observation indicated that the catalyst might decompose at high temperature. To avoid catalyst decomposition, we conducted the reaction at a lower temperature. However, at lower temperatures, the substrate solubility in toluene became a serious problem. Gratifyingly, changing the imine protecting group to benzenesulfonyl from *p*-toluenesulfonyl successfully resolved the solubility issues, and catalyst decomposition. Indeed, the use of benzenesulfonyl imine **4.29** as a coupling partner provided the desired product **4.31** in 94% yield (Table 4.4).

Table 4.4 Optimization table



Entry	X	Ar	Additive	Solvent	Temp (^{o}C)	Yield (%)
1	SbF_6	*p*-MePh	TPAA	DCE	24	8
2	BARF	*p*-MePh	TPAA	DCE	24	12
3	BARF	*p*-MePh	TPAA	DCE	40	21
4	BARF	*p*-MePh	TPAA	Toluene	80	42
5	BARF	*p*-MePh	*m*-Nitrobenzoic acid	Toluene	80	68
6	BARF	Ph	*m*-Nitrobenzoic acid	Toluene	80	62
7	BARF	Ph	*m*-Nitrobenzoic acid	Toluene	45	94

The optimized conditions were applied to asymmetric reductive coupling of acetylene and imines. Gratifyingly, the first chiral ligand screened, (*S*)-Cl,MeO-BIPHEP, was found to promote excellent levels of asymmetric induction to produce the desired allylic amine **4.31** in 83% yield with 97% ee (Scheme 4.5).

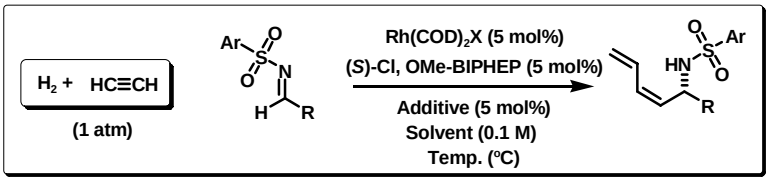


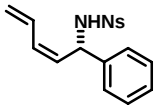
Scheme 4.5 Asymmetric reductive coupling of acetylene with compound **4.29**.

4.3.3 Substrate Scope

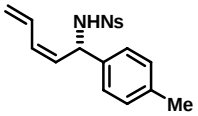
Under the optimized conditions, aromatic *N*-arylsulfonyl aldimines were found to engage in highly enantioselective couplings with gaseous acetylene to furnish (*Z*)-dienylallylic amines **4.32**-**4.43** in good yields as single geometrical isomers. However, benzaldimines possessing ortho substitution do not react efficiently. Heteroaryl *N*-arylsulfonyl aldimine also underwent the reductive coupling to produce the corresponding product **4.40** in 73% yield with excellent enantioselectivity. In this class of reductive coupling, the arylsulfonyl protecting group was chosen in response to issues of solubility and reactivity. Generally, increased yields were observed upon introduction of Na_2SO_4, which presumably prevents imine hydrolysis and the production of catalytically inactive hydroxyl-bridged dimmers of rhodium.[7] Indeed, in case of alkyl aldimines, the use of excess Na_2SO_4 (600 mol%) reproducibly provided the corresponding products **4.41**-**4.43** in good yields (Table 4.5).

Table 4.5 Enantioselective reductive coupling of acetylene with imines.[20]

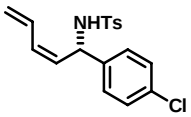




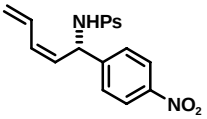
4.32, 86% yield
> 95:5 Z:E
93% ee



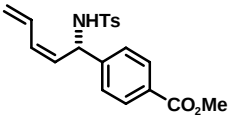
4.33, 71% yield
> 95:5 Z:E
98% ee



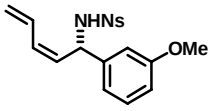
4.34, 74% yield
> 95:5 Z:E
95% ee



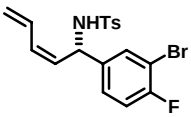
4.35, 83% yield
> 95:5 Z:E
97% ee



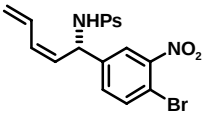
4.36, 75% yield
> 95:5 Z:E
95% ee



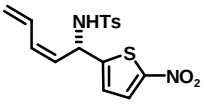
4.37, 72% yield
> 95:5 Z:E
97% ee



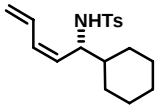
4.38, 70% yield
> 95:5 Z:E
97% ee



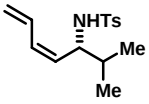
4.39, 71% yield
> 95:5 Z:E
94% ee



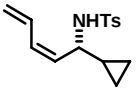
4.40, 73% yield
> 95:5 Z:E
95% ee



4.41, 68% yield
> 95:5 Z:E
97% ee



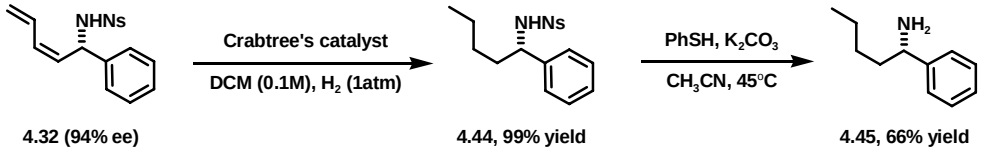
4.42, 70% yield
> 95:5 Z:E
98% ee



4.43, 65% yield
> 95:5 Z:E
97% ee

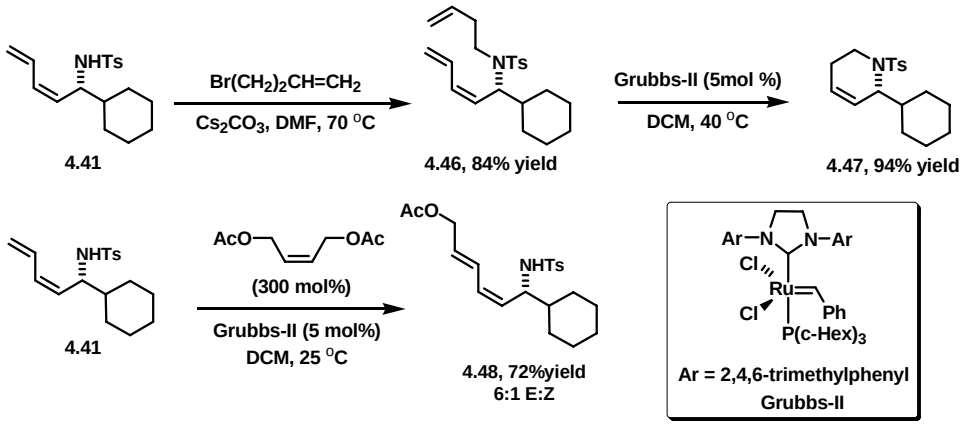
4.3.4 Elaboration of Reductive Coupling Products

To illustrate the unique features of the (*Z*)-dienyl side chain, a variety of selective transformations were conducted. First of all, exhaustive hydrogenation of compound **4.32** using Crabtree's catalyst followed by deprotection of **4.44** provided saturated compound **4.45** in 65% overall yield (Scheme 4.6). The reduced amine **4.45** was used for determining absolute stereochemical assignment by comparing to optical rotation value of an authentic sample ($[\alpha]_D$ of compound **4.45** = -17.2 (c = 0.67, DCM, 94% ee and $[\alpha]_D$ of an authentic sample of optically enriched material in literature = -17.4 (c = 1.19, DCM, 94% ee).[21]



Scheme 4.6 Determination of absolute configuration.

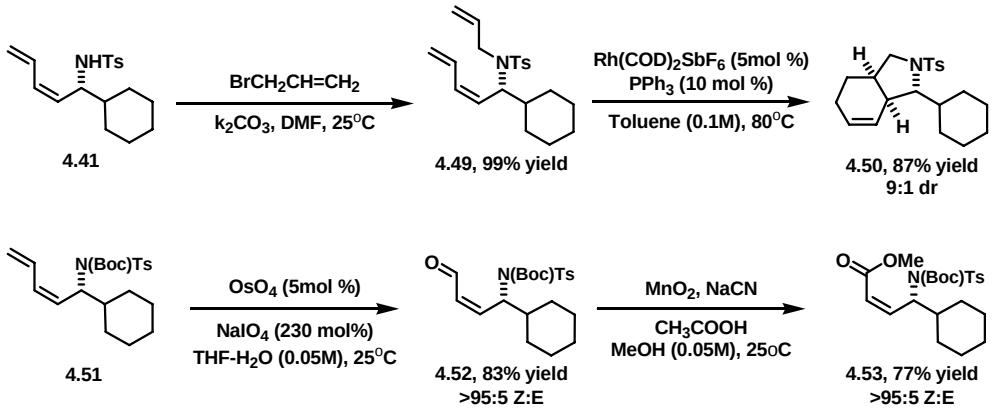
N-allylation of the diene product **4.41** followed by ring-closing metathesis of **4.46** using the second generation Grubbs' catalyst provided compound **4.47** in 94% yield.[22] Furthermore, functionalization of the diene terminus *via* cross-metathesis was explored. Exposure of the reductive coupling product **4.41** to cis-1,4-diacetoxy-2-butene in the presence of 5 mol% of the second generation Grubbs' catalyst provided the allylic acetate **4.48** in 72% yield as a 6:1 mixture of alkene stereoisomers (Scheme 4.7).



Scheme 4.7 Elaboration of coupling product *via* metathesis.

In order to utilize the diene functionality of the coupling products, rhodium-catalyzed intramolecular [4+2] cycloaddition was explored. *N*-homoallylation of the compound **4.41** provided compound **4.49** in 84% yield. Exposure of compound **4.49** to $Rh(COD)_2SbF_6$ in the presence of PPh_3 produced cycloaddition product **4.50** in 87% yield as a 9:1 mixture of diastereomers. The relative stereochemistry is assigned based on

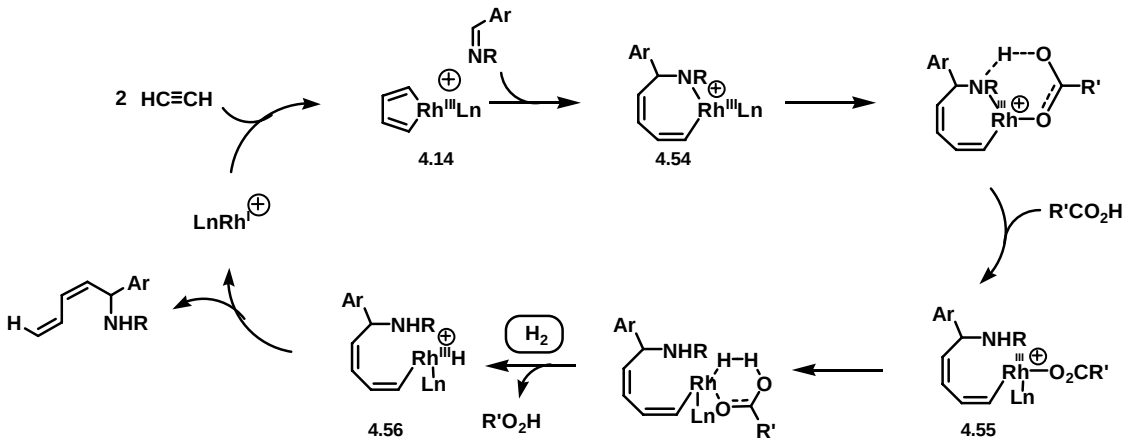
Livinghouse's studies.[23] Finally, site selective oxidative cleavage of compound **4.51** under Johnson-Lemieux conditions provided aldehyde **4.52** in 83% yield. Further oxidation of aldehyde **4.52** in the presence of MnO_2, NaCN, CH_3COOH, and MeOH provided methyl ester **4.53** in 77% yield without *cis-trans* isomerization (Scheme 4.8).[24]



Scheme 4.8 Elaboration of coupling product **4.51**.

4.3.5 Mechanistic Studies

Based on mechanistic studies of the multicomponent reductive coupling of acetylene and carbonyls,[9] a plausible catalytic mechanism is proposed. In the catalytic cycle, acetylene dimerization to form rhodacyclopentadiene **4.14** is followed by imine insertion[25] to furnish an intermediate **4.54**. Protonolytic cleavage of the rhodium-nitrogen bond in the intermediate **4.54** followed by σ-bond metathesis of the intermediate **4.55** with elemental hydrogen provides (alkenylhydrido)rhodium intermediate **4.56**, which upon C-H reductive elimination delivers the coupling product and the starting rhodium(I) complex to close the cycle (Scheme 4.9).



Scheme 4.9 Plausible catalytic cycle.

To further confirm our proposed catalytic mechanism, we performed ESI-MS studies. Initially, we prepared a sample for ESI-MS studies from the reductive coupling reaction of gaseous acetylene to imine **4.29** in the presence of *m*-nitrobenzoic acid and BIPHEP. Of particular interest is the ion of m/z 677 which matches the molecular weight expected for the rhodacyclopentadiene shown in the catalytic cycle. In addition, the other ion matches the calculated molecular weight of the rhodacycloheptadiene (m/z 967). However, the ion of m/z 1134 which matches the molecular weight expected for the intermediate **4.55** shown in the catalytic cycle was not observed. This result indicates that the life time of intermediate **4.55** in the catalytic cycle is not long enough to be detected by ESI-MS methods. These results are consistent with a highly increased reaction rate when *m*-nitrobenzoic acid is used as cocatalyst (Figure 4.6).

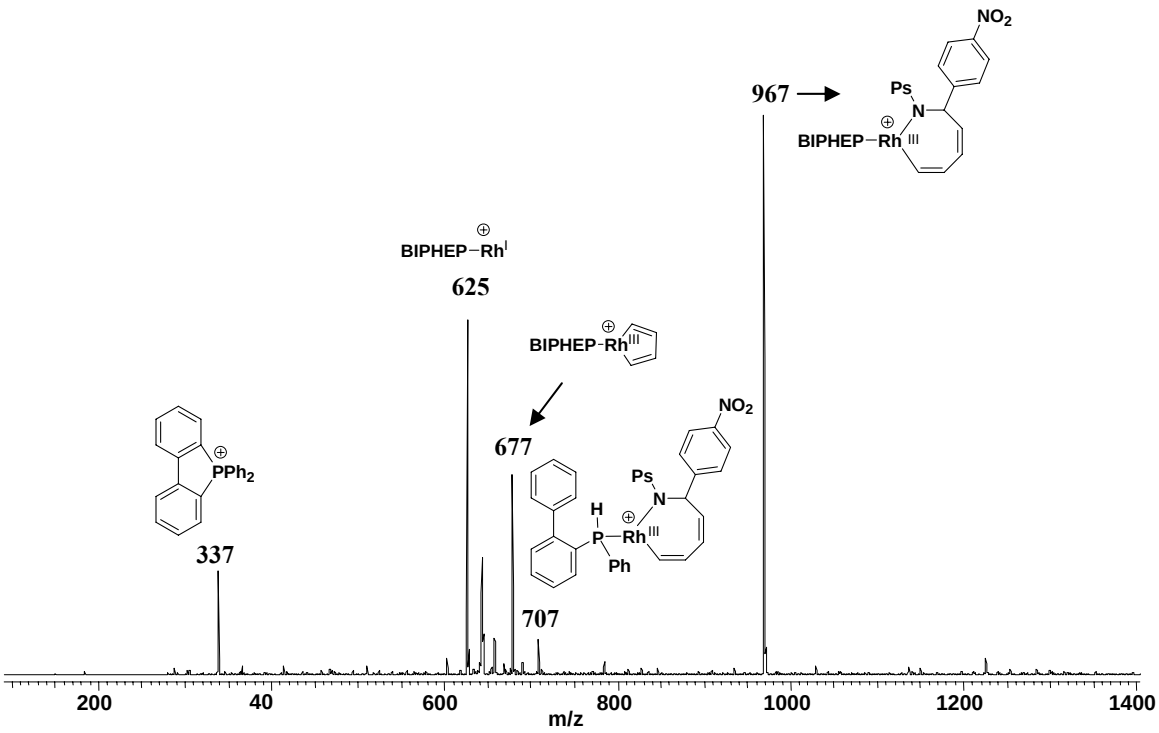


Figure 4.7 ESI Mass full scan spectrum for reductive coupling of acetylene to imine using *m*-nitrobenzoic acid cocatalyst.

Then we prepared a sample for ESI-MS studies from the reductive coupling reaction of gaseous acetylene to imine **4.29** in the presence of triphenylacetic acid and BIPHEP. Of particular interest is the ion of m/z 677 which matches the molecular weight expected for the rhodacyclopentadiene **4.53** shown in the catalytic cycle. In addition, two other ions match the calculated molecular weights of the rhodacycloheptadiene **4.54** (m/z 967) and the intermediate **4.55** (m/z 1255) obtained *via* protonolytic cleavage by triphenylacetic acid (Figure 4.7). In both cases, the ion corresponding to the coupling product of mono acetylene and mono imine (calculated molecular weight 941 Da) was not observed.

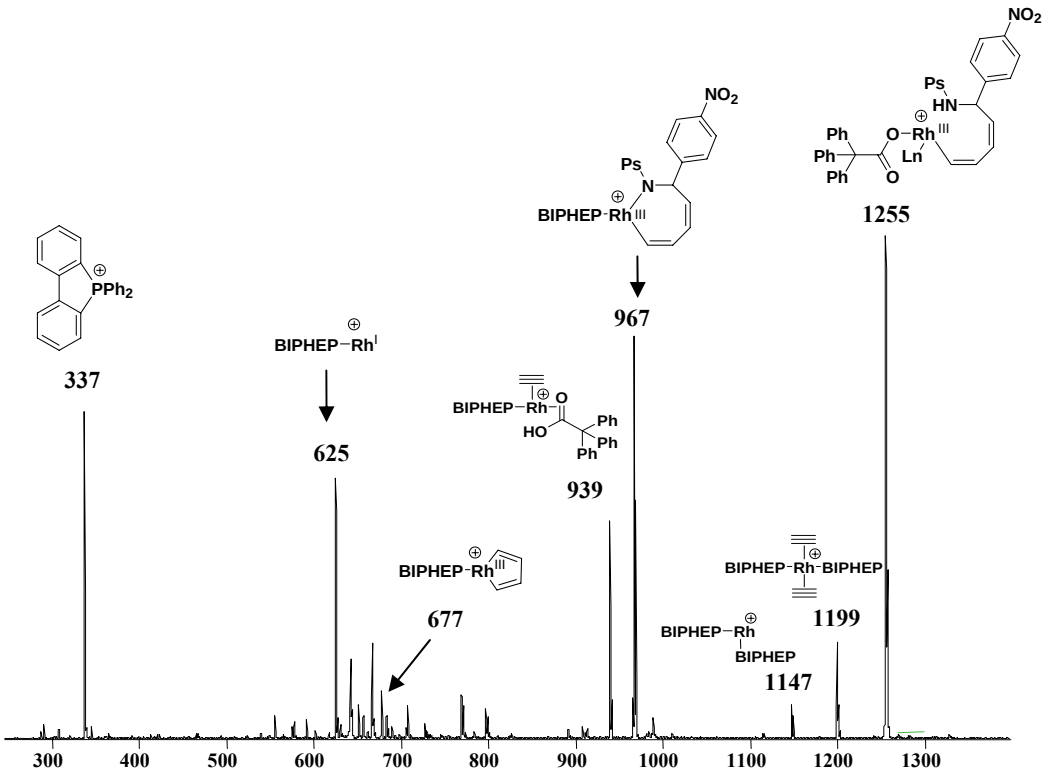


Figure 4.8 ESI Mass full scan spectrum for reductive coupling of acetylene to imine using triphenylacetic acid cocatalyst.

The structural assignment of the ion of m/z 1255 is corroborated by multi-stage collisional activated dissociation (CAD) (Figure 4.9). This ion dissociates by loss of 288 Da, consistent with the elimination of triphenylacetic acid to regenerate the oxarhodacycloheptadiene intermediate **4.54** (m/z 967). The structural assignment of the ion of m/z 967 is corroborated by multi-stage collisional activated dissociation (CAD) (Figure 4.10). This ion dissociates by loss of 260 Da, consistent with the elimination of one phenyl and diphenylphosphine to produce a decomposed rhodium complex (m/z 707).

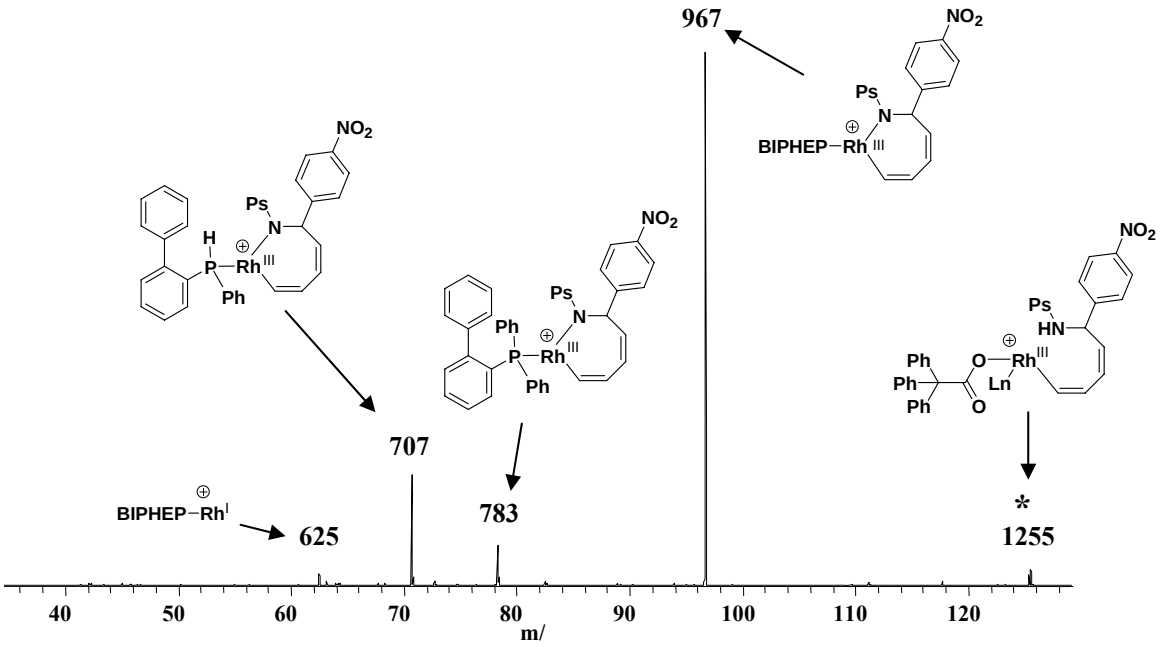


Figure 4.9 MS/MS spectrum of m/z 1255.

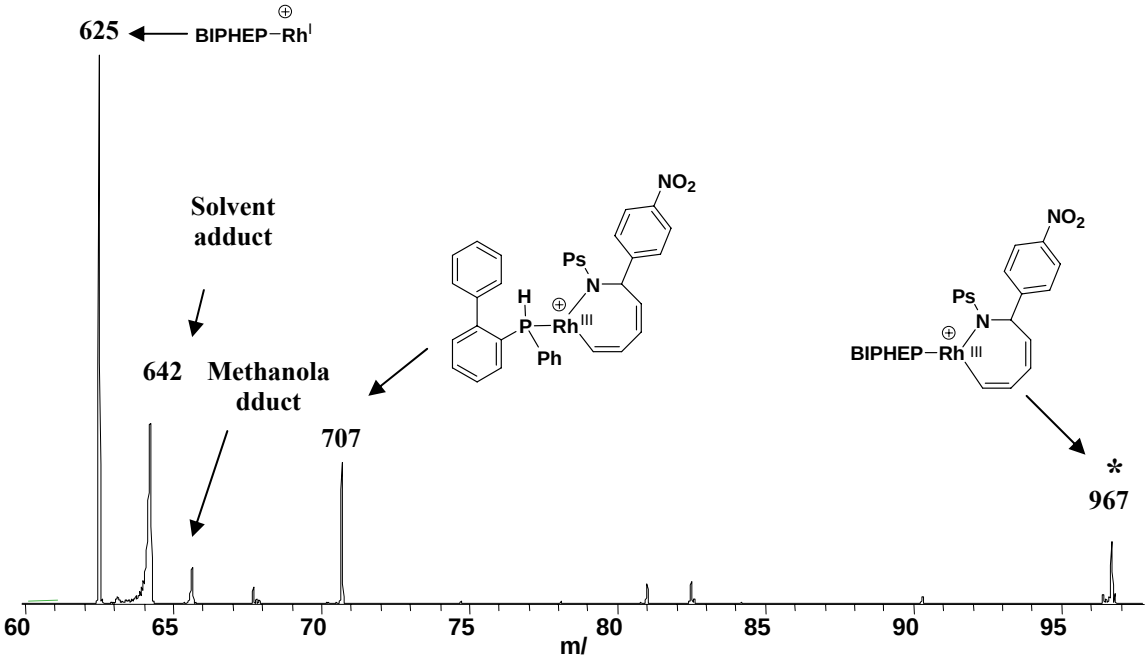


Figure 4.10 MS/MS spectrum m/z 967.

4.4 Reductive Coupling of Acetylene with Chiral Aldehydes: The Formal Synthesis of D-Hexoses

4.4.1 Introduction

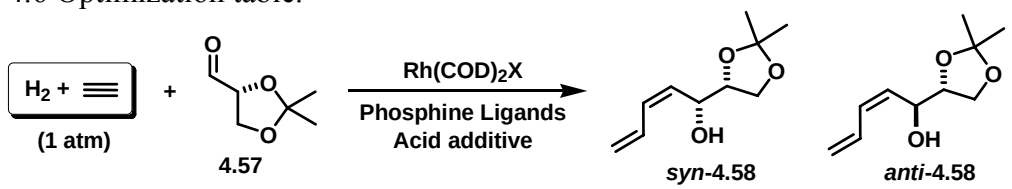
Enantiomerically pure 1,2-diols are important and commonly occurring functional group moeties in natural products[26] including carbohydrates, polyketides, and chiral ligands used in asymmetric catalysis.[27] Diastereoselective addition of alkenyl groups to chiral aldehydes is one of most powerful methods towards generating chiral allylic alcohols. The goal of the present study is to establish the viability of chiral catalyst-controlled doubly diastereoselective reductive coupling between acetylene and optically active chiral aldehydes.[28] If successful, such a strategy would provide selective access to 1,2-*syn*-products and 1,2-*anti*-products which are not readily obtainable using substrate-controlled diastereoselective reactions. Here, we report diastereoselective coupling of acetylene with chiral aldehydes, and application in the formal synthesis of natural D-hexoses.

4.4.2 Optimization

The reductive coupling between acetylene and (*R*)-glyceraldehyde **4.57** was investigated as a model reaction. The reductive coupling between acetylene and (*R*)-glyceraldehyde using achiral ligand BIPHEP provided the coupling products *syn*-**4.58** and *anti*-**4.58** in a 1:1 diasteromeric ratio. Next, a chiral catalyst system was employed in the reaction. Chiral ligand (*S*)-MeO-BIPHEP provided the desired product in 46% yield and a 1:4 diasteromeric ratio. To increase chemical yields, we applied the optimized conditions for the reductive coupling of acetylene and imines to this catalytic system. The

coupling product was obtained in 57% yield with a 1:5.7 diasteromeric ratio. By employing pentafluorobenzoic acid as cocatalyst, the yield of coupling product was increased to 79%. The diastereoselectivity and chemical yield were further improved by careful examination of reaction temperature. At 4 ^{o}C, the yield of **4.58** was increased to 83% with good *anti*-selectivity. We tested the reductive coupling using (*R*)-MeO-BIPHEP to obtain *syn*-selectivity. Gratifyingly, the use of (*R*)-MeO-BIPHEP provided the coupling product as predominantly the *syn* diastereomer (Table 4.6).

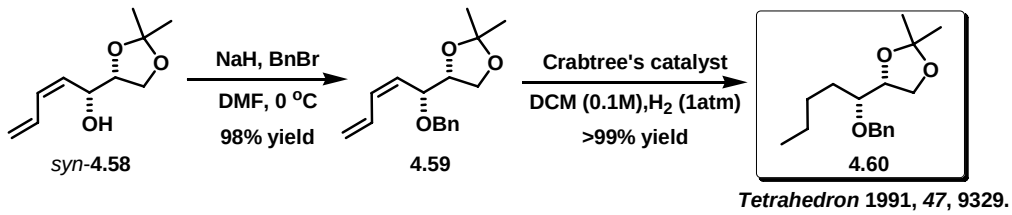
Table 4.6 Optimization table.



entry	ligand	X	solvent	acid additive	yield (%)	dr (*syn:anti*)
1	BIPHEP	SbF_6	DCE	Triphenylacetic acid	70	1:1
2	(S)-MeO-BIPHEP	SbF_6	DCE	Triphenylacetic acid	46	1:4
3	(S)-MeO-BIPHEP	BARF	Toluene	m-Nitrobenzoic acid	57	1:5.7
4	(S)-MeO-BIPHEP	BARF	Toluene	pentafluorobenzoic acid	79	1:5.4
5[a]	(S)-MeO-BIPHEP	BARF	Toluene	pentafluorobenzoic acid	83	1:6.7
6	(R)-MeO-BIPHEP	BARF	Toluene	pentafluorobenzoic acid	78	>20:1

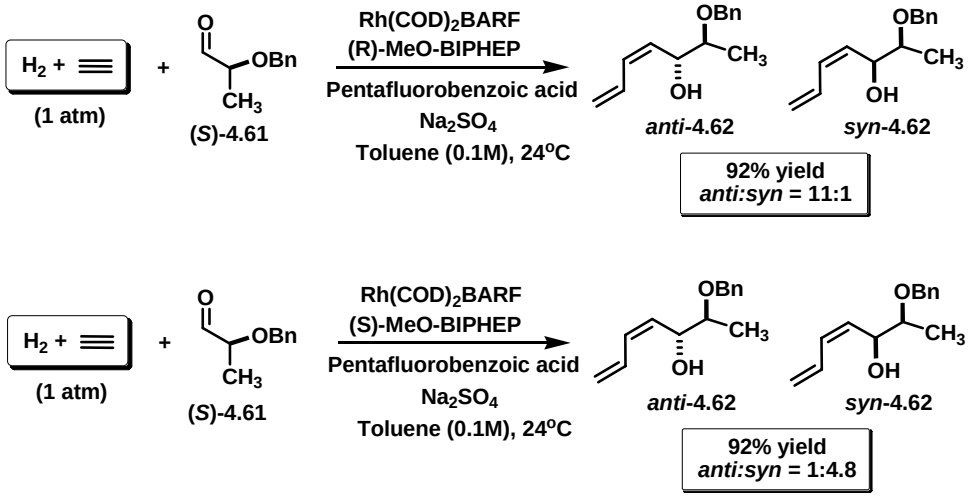
a: the reaction was performed at 4 ^{o}C.

To determine the relative stereochemistry, compound *syn*-**4.58** was further transformed. Benzylation of *syn*-**4.58** followed by exhaustive hydrogenation of **4.59** using Crabtree's catalyst provided compound **4.60** in 98% and 99% yield, respectively. By ^{1}H-NMR comparison with an authentic sample in the literature,[29] we confirmed the relative stereochemistry of the diol *syn*-**4.58** (Scheme 4.10).



Scheme 4.10 Determination of relative stereochemistry of *syn*-**4.58**.

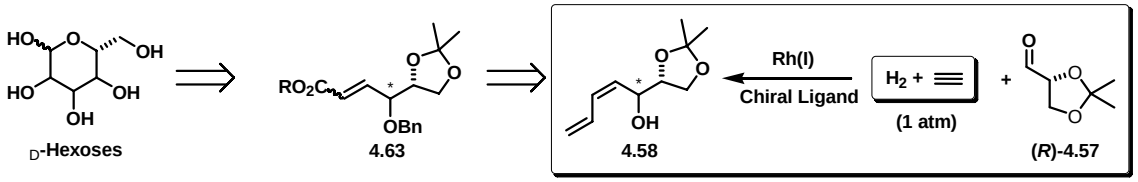
Under the optimized conditions, another chiral aldehyde was tested. Exposure of aldehyde (*S*)-**4.61** to reaction with acetylene in the presence of (*R*)-MeO-BIPHEP led to formation of the corresponding diastereomerically enriched diol **4.62** in 95% yield with good *syn*-diastereoselectivity. The reductive coupling of aldehyde (*S*)-**4.61** with acetylene in the presence of (*S*)-MeO-BIPHEP provided diol **4.62** in 92% yield and a moderate *anti*-diastereoselectivity (Scheme 4.11).



Scheme 4.11 Reductive coupling of acetylene with (*S*)-**4.61**.

4.4.3 A Versatile Route to Hexoses: Synthesis of the Key Intermediates

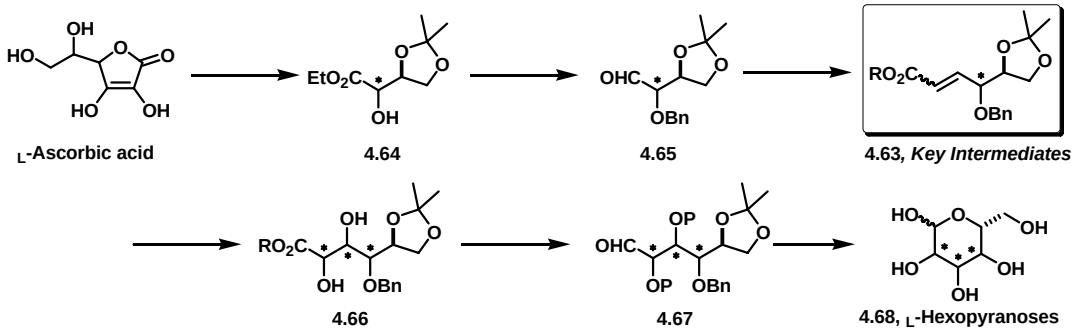
Hexose carbohydrates play vital roles in a diverse set of biological processes such as signal transduction, cognition, and immunal response. Given the importance of hexoses, the development of efficient methods for their synthesis has continuously received significant attention.[30] In this regard, we decided to explore the development of a practical method to access all eight $_{L}$-hexoses as well as $_{D}$-hexoses. We envisioned that the reductive coupling product **4.58** could be applied to the synthesis of $_{D}$-hexoses. A versatile route for the synthesis of $_{D}$-hexoses is presented in Scheme 4.12. Essential to this strategy is the rapid access of chiral key intermediates **4.63** and the utilization of these intermediates in the formal synthesis of all eight $_{D}$-hexoses (Scheme 4.12).



Scheme 4.12 General strategy for the synthesis of $_{D}$-hexoses.

In 2006, the Sasaki group reported diastereoselective synthesis of all eight $_{L}$-hexoses from $_{L}$-Ascorbic acid.[31] The strategy to synthesize all eight diastereopure $_{L}$-hexoses comprises the following major steps: (1) preparation of chiral aldehydes **4.65**, one of which involving Mitsunobu inversion, from α-hydroxy ester **4.64** that is in turn readily available from $_{L}$-ascorbic acid; (2) transformation of aldehyde **4.65** into four α,β-unsaturated esters **4.63** with the specified (*E*) or (*Z*) configuration via Wittig olefination reactions; (3) stereoselective dihydroxylation of each of the α,β-unsaturated esters **4.63,**

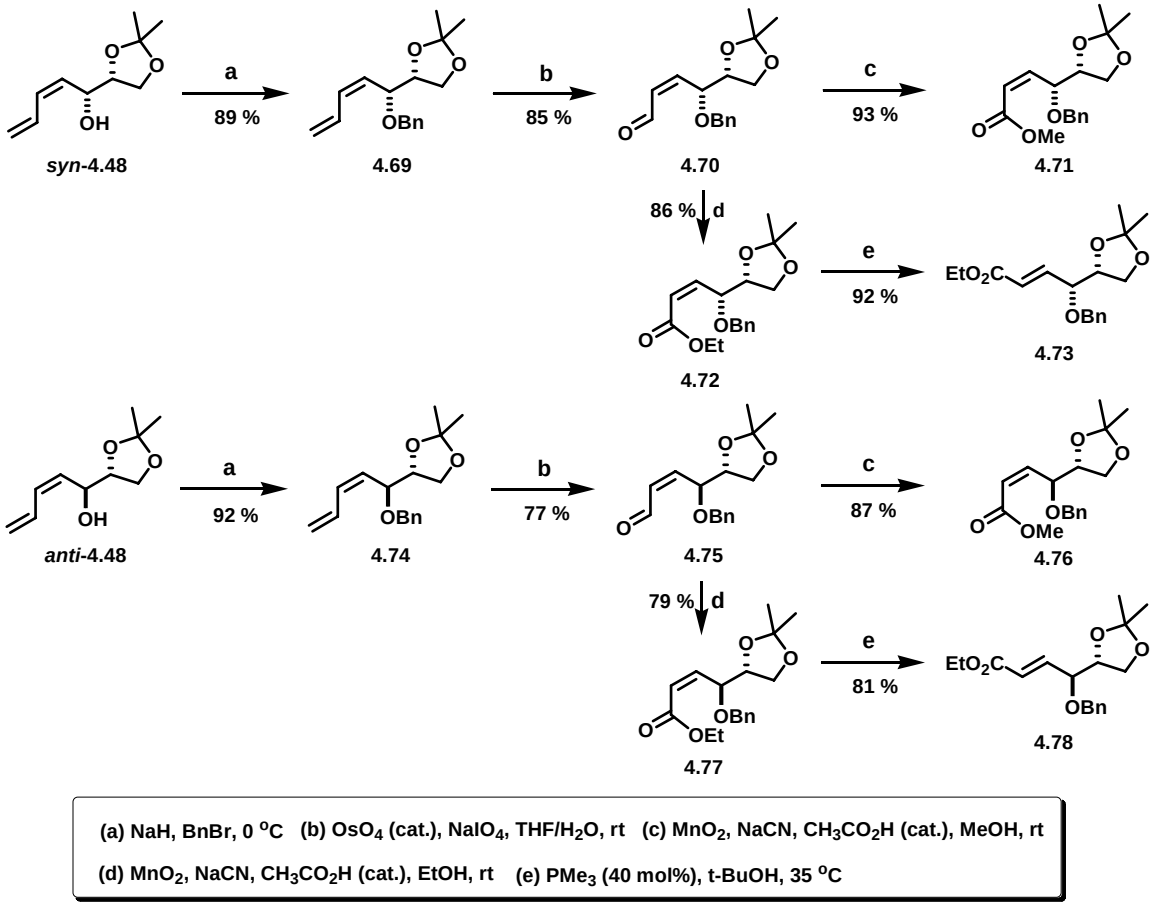
followed by partial reduction of resulting eight polyol esters **4.67**, and (4) cyclization of thus obtained aldehydes **4.67** to provide $_{L}$-hexopyranoses **4.68** (Scheme 4.13).



Scheme 4.13 Sasaki's strategy for the synthesis of $_{L}$-hexoses.

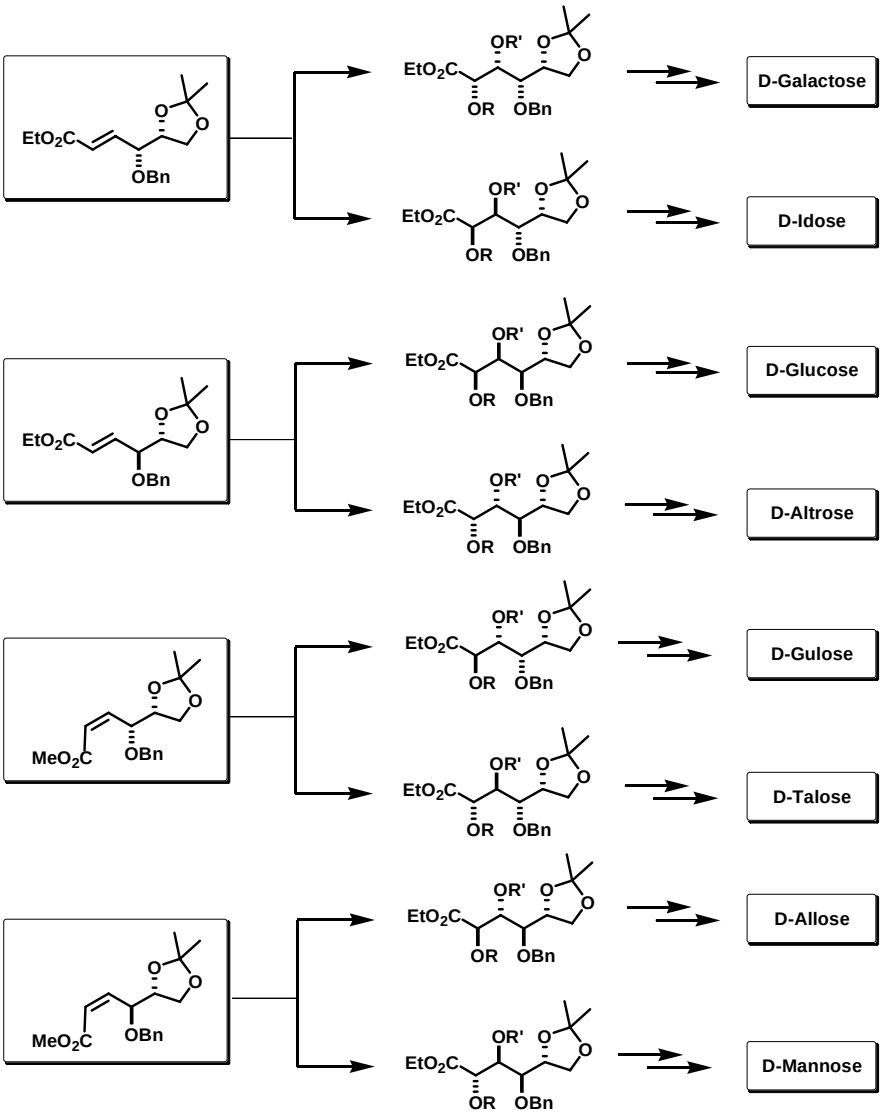
Our formal synthesis of $_{D}$-hexoses started with benzylation of newly generated secondary alcohols. Exposure of *syn*-**4.48** to benzylation conditions provided the compound **4.69** in 89% yield. The site selective oxidative cleavage of compound **4.69** under Johnson-Lemieux conditions provided aldehyde **4.70** in 85% yield without *cis-trans* isomerization. Further oxidation of aldehyde in presence of MnO_2, NaCN, CH_3COOH, and MeOH provided methyl ester **4.71** in 93% yield without alkene isomerization. Additionally, oxidation of aldehyde in presence of MnO_2, NaCN, CH_3COOH, and EtOH provided ethyl ester **4.72** in 86% yield. To obtain (*E*)-isomer **4.73**, we tried isomerization of (*Z*)-α,β-unsaturated ester **4.72** with LiI in ether.[32] Unfortunately, only starting material was recovered. The trimethylphosphine catalyzed isomerization was explored. Upon exposure of (*Z*)-α,β-unsaturated ester **4.72** to trimethylphosphine catalyst, the (*E*)-ester **4.73** was obtained in 50% yield along with almost 50% of starting material. Finally, we successfully optimized the isomerization reaction using trimethylphosphine as a catalyst and *tert*-butanol as solvent at 35 ^{o}C. The *cis-trans* isomerization of α,β-unsaturated thioester has been well documented in the literature.[33] However, *cis-trans* isomerization of α,β-unsaturated esters is relatively rare.[34] This result

displays the feasibility of phosphine-catalyzed *cis-trans* isomerization of α,β-unsaturated esters. Using optimized conditions for *syn*-**4.48**, the *anti*-**4.48** was also successfully transformed to the corresponding α,β-unsaturated esters **4.76** and **4.78** with good to excellent yields (Scheme 4.14).



Scheme 4.14 Synthesis of key intermediates for D-hexoses.

Four esters **4.71**, **4.73**, **4.76**, and **4.78** are enantiomers of four key intermediates used in Sasaki's synthesis of L-hexoses. As such, the syntheses of esters **4.71**, **4.73**, **4.76**, and **4.78** represent a formal synthesis of D-hexoses (Scheme 4.15).



Scheme 4.15 Sasaki's $_{L}$-hexose syntheses from esters.

4.5 SUMMARY AND CONCLUDING REMARKS

It was found that gaseous acetylene couples to conventional aldehydes under hydrogenation conditions to furnish products of Z-butadienylation. Moreover, this methodology is successfully extended to asymmetric reactions. ESI-MS studies strongly support our proposed catalytic mechanism; inferring an oxidative-coupling followed by hydrogenative termination pathway. Likewise, the highly enantioselective catalytic vinylation of aldimines is achieved. This protocol does not employ preformed organometallic reagents, nor does it generate stoichiometric byproducts.

The multicomponent coupling of acetylene and chiral aldehydes affords 1,2-diols in good yields with good to excellent diastereoselecitivity. In particular, catalyst-controlled diastereoselective coupling allows the selective preparation of both the *syn*-adduct and *anti*-adduct. This methodology has been successfully applied to the formal synthesis of all eight $_{D}$-hexoses. Finally, one can also gain access to all eight $_{L}$-hexose when (S)-glyceraldehyde instead of (R)-glyceraldehyde is employed in this method.

4.6 EXPERIMENTAL SECTION

4.6.1 GENERAL

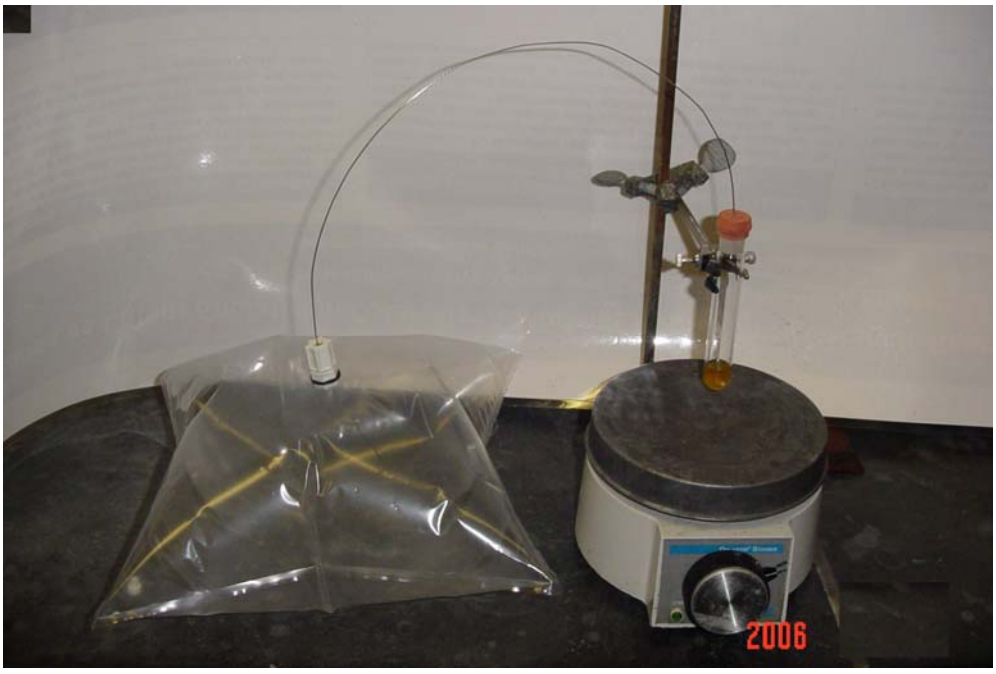
All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. Dichloroethane (DCE) was distilled from calcium hydride. Toluene was distilled from sodium and benzophenone. Triphenylacetic acid, *m*-nitro-benzoic acid, and pentafluorobenzoic acid were used as received from Aldrich. BIPHEP and (S)-Cl,MeO-BIPHEP were used as received from Strem Chemicals. (R)-MeO-BIPHEP and (S)-MeO-BIPHEP were used as received from Aldrich. Acetylene Gas was used as received from PRAXAIR (Atomic Absorption Grade). $[Rh(COD)_2]BF_4$, $[Rh(COD)_2]SbF_6$, and $[Rh(COD)_2]BARF$ were prepared in analogy with the previously reported procedures. 2,3-*O*-isopropylidene-$_D$-glyceraldehyde and (R)-*O*-benzyllacta-aldehyde were prepared in analogy with the previously reported procedures. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M + 1) or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian Gemini (400 MHz or 300MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (pip) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded with a Varian Gemini 300 (75 MHz) or 400 (100 MHz) spectrometer. Chemical shifts are reported in

delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

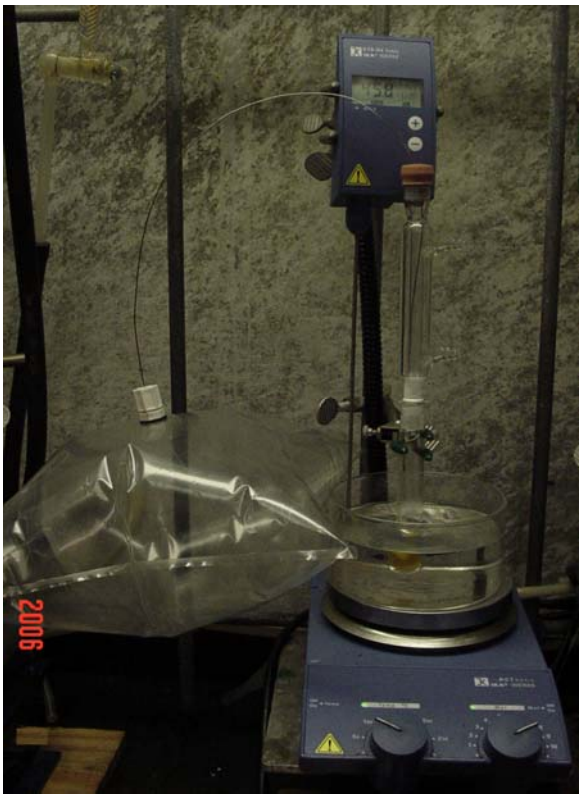
All the ESI-MS/MS work was conducted with a Thermo LCQ Duo quadrupole ion trap mass spectrometer equipped with an electrospray ionization source (San Jose, CA). The flow rate of the reaction mixtures (estimated ~2 μM) was 5 μL/min. The ESI spray voltage was +4.5 kV. The heated capillary temperature was set at 80 ^{o}C to minimize polymerization. One microliter of the reaction mixture was removed from the reaction vessel at specific intervals, diluted 5,000 times with methanol, and immediately infused into the LCQ instrument.

4.6.2 Experimental Apparatus

For reactions at room temperature



For reactions at 45 ^{o}C.



1) Reaction Vessel: 2.0cm (Diameter) * 13.0cm (Length)
2) Gas bag : Tedlar® gas sampling bag (Aldrich)
3) Cannula (Double-tipped needle): 24 in.(Length) – 20 (gauge)

4.6.3 Multicomponent Reductive Coupling of Acetylene and Carbonyls

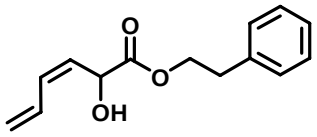
Representative Procedure 1 for the Coupling Products 4.2, 4.3, 4.4, 4.5, 4.9, 4.10, 4.11, 4.12a, and 4.13 ([$Rh(COD)_2$]SbF_6 as catalyst; with Na_2SO_4)

[$Rh(COD)_2$]SbF_6 (5.5 mg, 0.01 mmol, 5 mol%), BIPHEP (5.3 mg, 0.01 mmol, 5 mol%), triphenylacetic acid (4.4 mg, 0.015 mmol, 7.5 mol%), and Na_2SO_4 (58 mg, 0.4 mmol, 200 mol%) and DCE (1.2 mL) were added to a reaction vessel and then stirred for 30 minutes at room temperature. The mixture of hydrogen and acetylene gas (approximately 1:1 mixture) was introduced into the solution *via* cannula and then a solution of carbonyl substrate **4.1** (36mg, 0.2 mmol, 100 mol%) in DCE (0.8 mL) was

added to a reaction vessel. The mixture was stirred at room temperature under the 1 atm of hydrogen and acetylene gas mixture for 72 hours. The title compound was purified by flash column chromatography (R_f = 0.3, Pentane/Ether = 4/1) to afford 31.4 mg of compound **4.2** as a colorless oil (68 % yield).

Representative Procedure 2 for the Coupling Products 4.6, 4.7, and 4.8 ([Rh(BIPHEP) (NBD)]SbF_6 as catalyst; without Na_2SO_4)

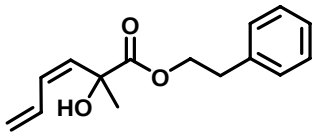
[Rh(BIPHEP)(NBD)]SbF_6 (9.6mg, 0.01 mmol, 5 mol%), triphenylacetic acid (2.9 mg, 0.01 mmol, 5 mol%), and DCE (1.2 mL) were added to a reaction vessel and then stirred for 30 minutes at room temperature. The mixture of hydrogen and acetylene gas (approximately 1:1 mixture) was introduced into the solution *via* cannula and then a solution of carbonyl substrate (41.6mg, 0.2 mmol, 100 mol%) in DCE (0.8 mL) was added to a reaction vessel. The mixture was stirred at 45 ^oC under the 1 atm of hydrogen and acetylene gas mixture for 42 hours. The title compound was purified by flash column chromatography (R_f = 0.15, Hexane/DCM = 1/1.5 and then DCM only) to afford 29.9 mg of the coupling product **4.6** as a colorless oil (57 % yield).



4.2

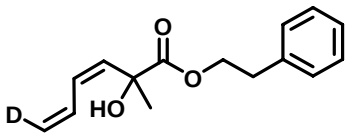
(*Z*)-2-Hydroxy-hexa-3,5-dienoic acid phenethyl ester (4.2). Representative procedure 1; R_f = 0.3, Pentane/Ether = 4/1; colorless oil. ^1H NMR (400 MHz, $CDCl_3$): 7.32 – 7.18 (m, 5H), 6.72 (dt, *J* = 16.4, 10.5 Hz, 1H), 6.21 (t, *J* = 10.9 Hz, 1H), 5.38 – 5.27 (m, 2H), 5.04 (dd, *J* = 3.2, 1.0 Hz, 1H), 4.45 – 4.34 (m, 2H), 2.95 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.5, 155.9, 138.6, 132.1, 130.7, 121.4, 79.7, 76.7, 53.5, 37.4, 28.6,

25.1. HRMS Calcd. for $C_{14}H_{17}O_3$ (M+1): 233.1178, Found: 233.1171. FTIR(neat): 3465, 3028, 2958, 1738, 1603, 1592, 1497, 1454, 1434, 1384, 1193, 1086, 1021, 996, 915, 815.



4.3

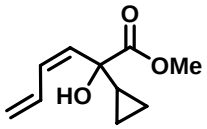
(*Z*)-2-Hydroxy-2-methyl-hexa-3,5-dienoic acid phenethyl ester (4.2). Representative procedure 1; R_f = 0.2, Hexane/DCM = 1/1; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.33 – 7.20 (m, 5H), 7.06 (dtd, *J* = 15.6, 10.7, 1.1 Hz, 1H), 6.03 (t, *J* = 11.6 Hz, 1H), 5.48 (dd, 11.6, 0.8 Hz, 1H), 5.21 (dd, *J* = 12.4, 2.0 Hz, 1H), 5.19 – 5.17 (m, 1H), 4.45 – 4.36 (m, 2H), 3.29 (s, br, 1H), 2.97 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.9, 137.2, 132.6, 132.1, 130.9, 128.9, 128.5, 126.7, 120.4, 74.9, 66.6, 34.9, 27.8. HRMS Calcd. for $C_{15}H_{18}O_3$ (M): 246.1256, Found: 246.1257. FTIR(neat): 3497, 3026, 2983, 2931,1730, 1692, 1603, 1497, 1454, 1367, 1244, 1185, 1121, 1084, 1030, 973, 911, 749, 700, 663.



***deuterio*-4.3**

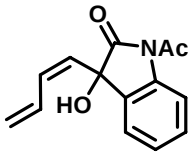
(*Z*)-2-Hydroxy-2-methyl-hexa-3,5-dienoic acid phenethyl ester (*deuterio*-4.3). Represenatative procedure 1; R_f = 0.2, Hexane/DCM = 1/1; colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 – 7.20 (m, 5H), 7.06 (t, *J* = 10.8, 1H), 6.03 (t, *J* = 11.4 Hz, 1H), 5.48 (d, 11.6, 1H), 5.17 (d, *J* = 10.0 Hz, 1H), 4.45 – 4.36 (m, 2H), 3.36 (s, br, 1H), 2.97 (t, *J* =

7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 175.9, 137.2, 132.5, 132.1, 130.9, 128.9, 128.5, 126.7, 120.4, 1201.1, 120.0, 74.9, 66.6, 34.9, 27.8. HRMS Calcd. for $C_{15}H_{18}DO_3$ (M+1): 248.1397, Found: 248.1403. FTIR(neat): 3497, 3026, 2983, 2931, 1730, 1692, 1603, 1497, 1454, 1367, 1244, 1185, 1121, 1084, 1030, 973, 911, 749, 700, 663.



4.4

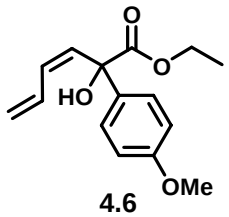
(*Z*)-2-Cyclopropyl-2-hydroxy-hexa-3,5-dienoic acid methyl ester (4.4). Representative procedure 1; . R_f = 0.3, Pentane/Ether = 8/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.02 (dtd, *J* = 16.8, 10.7, 1.2 Hz, 1H), 6.10 (t, *J* = 11.4 Hz, 1H), 5.61 (dd, 11.6, 0.8 Hz, 1H), 5.23 – 5.16 (m, 2H), 3.83 (s, 3H), 3.18 (s, br, 1H), 1.33 – 1.27 (m, 1H), 0.61 -0.54 (m, 1H), 0.48 – 0.39 (m, 2H), 0.37 – 0.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 176.5, 132.9, 132.7, 129.8, 120.3, 75.4, 75.1, 53.3, 53.3, 19.7, 0.65, 0.15. HRMS Calcd. for $C_{10}H_{15}O_3$ (M+1): 183.1021, Found: 184.1024. FTIR(neat): 3505, 3086, 3011, 2953, 2805, 1729, 1640, 1589, 1435, 1367, 1251, 1180, 1025, 910, 827.



4.5

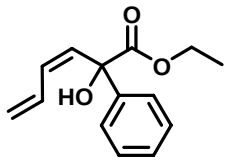
(*Z*)-1-Acetyl-3-buta-1,3-dienyl-3-hydroxy-1,3-dihydro-indol-2-one (4.5). Representative procedure 1; R_f = 0.2, Hexane/EA = 5/1; yellowish brown solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (d, *J* = 8.4 Hz, 2H), 7.41 (ddd, *J* = 7.5, 1.3, 0.7 Hz, 1H), 7.24 (td, *J* =

7.5, 1.1 Hz, 1H), 6.65 (dtd, *J* = 16.8, 11.4, 1.2 Hz, 1H), 6.21 (t, *J* = 11.6 Hz, 1H), 5.53 (s, 1H), 5.50 (d, *J* = 0.8, 1H), 5.28 (dt, *J* = 16.4, 0.8 Hz, 1H), 5.22 (d, J = 9.6 Hz), 3.14 (s, br, 1H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 177.3, 170.7, 139.5, 134.3, 131.8, 130.5, 130.1, 127.8, 126.1, 124.5, 122.4, 117.0, 76.9, 26.5. HRMS Calcd. for $C_{14}H_{14}NO_3$ (M+1): 244.0974, Found: 244.0975. FTIR(neat): 3421, 2997, 2945, 1771, 1713, 1605, 1464, 1372, 1334, 1302, 1270, 1165, 1102, 1034, 1014, 912, 854, 756, 693. MP 108 – 109 ^{o}C



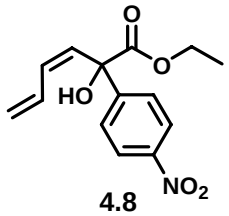
4.6

(*Z*)-2-Hydroxy-2-(4-methoxy-phenyl)-hexa-3,5-dienoic acid ethyl ester (4.6). Representative procedure 2; R_f = 0.15, Hexane/DCM = 1/1.5 and then DCM only; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.44 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.89 (dtd, *J* = 16.8, 10.6, 1.2 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.21 (t, *J* = 11.4 Hz, 1H), 5.97 (dd, 11.6, 0.8 Hz, 1H), 5.20 (dt, *J* = 16.8, 1.1 Hz, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 4.29 – 4.15 (m, 2H), 4.03 (s, br, 1H), 3.78 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.9, 159.2, 134.5, 133.4, 133.2, 130.4, 127.3, 120.5, 113.6, 78.1, 62.8, 55.2, 13.9. HRMS Calcd. for $C_{15}H_{19}O_4$ (M+1): 263.1283, Found: 263.1285. FTIR(neat): 93, 3082, 2979, 2933, 2835, 1724, 1607, 1582, 1508, 1463, 1442, 1367, 1298, 1247, 1175, 1084, 1033, 915, 830.



4.7

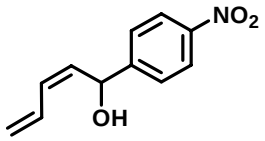
(*Z*)-2-Hydroxy-2-phenyl-hexa-3,5-dienoic acid ethyl ester (4.7). Representative procedure 2; R_f = 0.25, Hexane/DCM = 1/1.5; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.53 (d, *J* = 7.6 Hz, 2H), 7.35 – 7.27 (m, 3H), 6.89 (dt, *J* = 16.8, 10.6 Hz, 2H), 6.21 (t, *J* = 11.2 Hz, 1H), 5.99 (d, 11.6, 1H), 5.20 (d, *J* = 17.2, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 4.30 – 4.16 (m, 2H), 4.07 (s, br, 1H), 3.78 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.9, 142.7, 133.8, 133.4, 130.5, 128.5, 128.1, 126.2, 120.8, 78.7, 63.2, 14.2. HRMS Calcd. for $C_{14}H_{16}O_3$ (M): 232.1099, Found: 232.1101. FTIR(neat): 3495, 2982, 1726, 1588, 1492, 1368, 1297, 1243, 1164, 1095, 11068, 1029, 1004, 913.



4.8

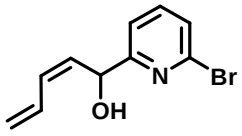
(*Z*)-2-Hydroxy-2-(4-nitro-phenyl)-hexa-3,5-dienoic acid ethyl ester (4.8). Represenative procedure 2; R_f = 0.2, Hexane/DCM = 1/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 2H), 6.78 (dt, *J* = 16.8, 10.6 Hz, 1H), 6.26 (t, *J* = 11.2 Hz, 1H), 6.00 (d, 11.2 Hz, 1H), 5.25 (d, *J* = 16.8, 1H), 5.19 (d, *J* = 10.0 Hz, 1H), 4.34 – 4.19 (m, 2H + 1H), 4.03 (s, br, 1H), 3.78 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 147.5, 134.6, 132.5, 129.1, 127.2, 123.4,

121.7, 77.9, 63.6, 13.9. HRMS Calcd. for $C_{14}H_{16}NO_5$ (M+1): 278.1028, Found: 278.1028. FTIR(neat): 3484, 3083, 2978, 2923, 2852, 1730, 1605, 1594, 1521, 1489, 1347, 1298, 1244, 1173, 1088, 1029, 1005, 917, 854, 829, 735, 702.



4.9

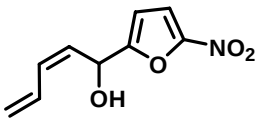
(*Z*)-1-(4-Nitro-phenyl)-penta-2,4-dien-1-ol (4.9). Representative procedure 1; R_f = 0.3, Hexane/EA = 5/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (d, *J* = 9.2 Hz, 2H), 7.53 (d, *J* = 9.2 Hz, 1H), 6.68 (dtd, *J* = 16.8, 10.8, 1.2 Hz, 1H), 6.17 (t, *J* = 10.9, 1H), 5.50 (tdd, *J* = 6.3, 2.0, 1.4 Hz, 1H) 5.34 (dt, *J* = 16.4, 0.8 Hz, 1H), 5.30 (d, *J* = 10.2 Hz, 1H), 2.35 (s, br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 150.1, 147.1, 131.7, 131.6, 130.8, 126.5, 123.7, 121.4, 68.8. HRMS Calcd. for $C_{11}H_{12}NO_3$ (M+1): 206.0817, Found: 206.0820. FTIR(neat): 3386, 3083, 3012, 2918, 1854, 1598, 1518, 1345, 1187, 1108, 1046, 1003, 917, 854, 831, 745, 704, 669.



4.10

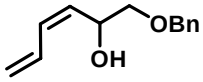
(*Z*)-(6-Bromo-pyridin-2-yl)-penta-2,4-dien-1-ol (4.10). Representative procedure 1; R_f = 0.3, Hexane/EA = 6/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.51 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 6.81 (dt, *J* = 16.8, 10.8 Hz, 1H), 6.21 (t, *J* = 11.0 Hz, 1H), 5.62 (d, *J* = 9.2 Hz, 1H),), 5.48 (t, *J* = 9.8 Hz, 1H), 5.34 (dd, *J*

= 9.2 Hz, 16.8, 0.8, 1H), 5.26 (d, J = 10.0 Hz, 1H), 3.81 (s, br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 162.1, 141.0, 139.2, 132.1, 131.4, 126.9, 120.6, 119.6, 68.7. HRMS Calcd. for $C_{10}H_{11}NOBr$ (M): 240.0024, Found: 240.0023. FTIR(neat): 3381, 3084, 2986, 2924, 1580, 1554, 1434, 1404, 1227, 1159, 1121, 1050, 993, 914, 788, 741, 710, 649.



4.11

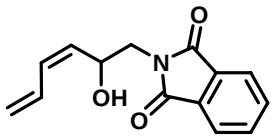
(*Z*)-1-(5-Nitro-furan-2-yl)-penta-2,4-dien-1-ol (4.11). Representative procedure 1; R_f = 0.2, DCM only and then Hexane/EA = 2/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.21 (d, *J* = 3.6 Hz, 1H), 6.68 (dt, *J* = 16.8, 10.7 Hz, 1H), 6.45 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.21 (t, *J* = 11.0, 1H), 5.66 (d, *J* = 8.4 Hz, 1H), 5.59 (t, *J* = 9.6 Hz, 1H), 5.06 (d, *J* = 16.8 Hz, 1H), 5.26 (d, *J* = 10.0 Hz, 1H), 2.67 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 158.6, 133.7, 130.6, 127.1, 121.9, 112.5, 109.8, 63.8. HRMS Calcd. for $C_9H_{10}NO_4$ (M+1): 196.0610, Found: 196.0614. FTIR(neat): 3382, 3121, 2918, 2850, 1584, 1526, 1495, 1354, 1239, 1017, 967, 810.



4.12a

(*Z*)-1-Benzyloxy-hexa-3,5-dien-2-ol (4.12a). Representative procedure 1; R_f = 0.3, Hexane/EA = 4/1; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.38 -7.26 (m, 5H), 6.62 (dtd, *J* = 16.8, 10.5, 0.9 Hz, 1H), 6.10 (t, *J* = 11.1 Hz, 1H), 5.39 (dd, *J* = 10.2, 9.0 Hz, 1H), 5.26 (d, *J* = 16.5 Hz, 1H), 5.18 (d, *J* = 10.2 Hz, 1H), 4.76 (td, *J* =8.2, 2.5 Hz, 1H),

4.56 (s, 2H), 3.49 (dd, *J* =9.6, 3.3 Hz, 1H), 3.39 (dd, *J* =9.8, 8.3 Hz, 1H), 2.26 (s, br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 137.7, 132.2, 131.7, 129.3, 128.5, 127.8,127.8, 119.8, 73.8, 73.4, 67.2. HRMS Calcd. for $C_{21}H_{23}NO_9$ (M): 433.1373, Found: 433.1374. FTIR(neat): 3418, 3085, 3029, 2914, 2859, 1593, 1495, 1453, 1363, 1315, 1208, 1104, 1074, 1027, 999, 910, 769.



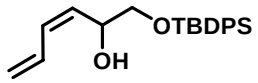
4.13

(*Z*)-2-(2-Hydroxy-hexa-3,5-dienyl)-isoindole-1,3-dione (4.13). Representative procedure 1; R_f = 0.3, Hexane/EA = 3/1; white solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.85 – 7.80 (m, 2H), 7.73 -7.67 (m, 2H), 6.63 (dt, *J* = 16.8, 10.7 Hz, 1H), 6.10 (t, *J* = 11.0 Hz, 1H), 5.44 (t, *J* = 9.6 Hz, 1H), 5.22 (d, *J* = 8.4, 1H), 5.15 (d, *J* = 9.9 Hz, 1H), 4.97 – 4.90 (m, 1HB), 3.84 (dd, *J* = 13.8, 7.8 Hz, 1H), 3.73 (dd, *J* = 14.1, 5.0 Hz, 1H), 2.25 (s, br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.7, 134.1, 132.6, 131.9, 131.3, 130.2, 123.4, 120.4, 66.5, 43.7. HRMS Calcd. for $C_{14}H_{14}NO_3$ (M+1): 244.0974, Found: 244.0970. FTIR(neat): 3466, 2927, 2853, 1772, 1713, 1613, 1467, 1429, 1395, 1332, 1190,1068, 1035, 10202, 914, 794. MP 99 – 100 ^{o}C

Representative Procedure for Asymmetric Reductive Coupling

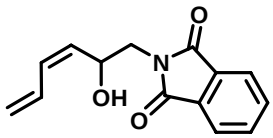
General procedure 1 was used. $[Rh(COD)_2]$BARF (11.8 mg, 0.01 mmol, 5 mol%), (*R*)-MeO-BIPHEP (5.9 mg, 0.01 mmol, 5 mol%), triphenylacetic acid (4.4 mg,

0.015 mmol, 7.5 mol%), and Na_2SO_4 (58 mg, 0.4 mmol, 200 mol%) and DCE (1.2 mL) were added to a reaction vessel and then stirred for 30 minutes at room temperature. The mixture of hydrogen and acetylene gas (approximately 1:1 mixture) was introduced into the solution *via* cannula and then a solution of carbonyl substrate (60.0mg, 0.2 mmol, 100 mol%) in DCE (0.8 mL) was added to a reaction vessel. The mixture was stirred at room temperature under the 1 atm of hydrogen and acetylene gas mixture for 72 hours. The title compound was purified by flash column chromatography.



4.12b

(*Z*)-1-(tert-Butyl-diphenyl-silanyloxy)-hexa-3,5-dien-2-ol (4.12b). R_f = 0.3, Hexane /DCM = 1/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.68 - 7.64 (m, 4H), 7.45 - 7.36 (m, 6H), 6.39 (dtd, *J* = 16.8, 10.6, 1.1 Hz, 1H), 6.05 (t, *J* = 11.2 Hz, 1H), 5.35 (dd, *J* = 10.2, 9.2 Hz, 1H), 5.19 (dt, *J* = 16.8, 0.8 Hz, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 4.66 – 4.61 (m, 1H), 3.62 (dd, *J* =10.4, 3.6 Hz, 1H), 3.55 (dd, *J* =10.2, 8.2 Hz, 1H), 2.64 (d, *J* =2.8 Hz, 1H), 1.07 (s, 9H). ^{13}C NMR (70 MHz, $CDCl_3$): 135.5, 135.5, 133.1, 132.9, 132.2, 131.8, 129.9, 129.8, 129.3, 127.8, 127.8, 119.5, 68.8, 67.4, 26.8, 19.2. FTIR(neat): 3418, 3070, 2929, 2857, 1960, 1896, 1825, 1589, 1471, 1427, 1390, 1361, 1313, 1221, 1188, 1112, 1056, 998, 909, 823, 739, 701, 613. HPLC (Chiralcel OD-H column, 0.5% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{major} = 36.7 min, t_{minor} = 49.3 min; ee = 89%.

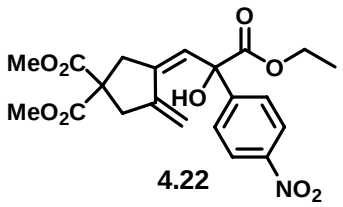


4.13

(*Z*)-2-(2-Hydroxy-hexa-3,5-dienyl)-isoindole-1,3-dione (4.13). R_f = 0.3, Hexane /EA = 3/1; white solid ;HPLC (Chiralcel AD-H column, 11% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{major} = 44.2 min, t_{minor} = 47.6 min; ee = 88%.

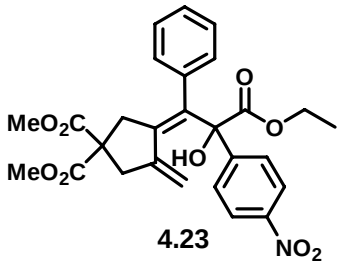
Representative Procedures for Reductive Coupling of 1,6-Diyne with Carbonyl

$[Rh(COD)_2]SbF_6$ (5.5 mg, 0.01 mmol, 5 mol%), BIPHEP (5.3 mg, 0.01 mmol, 5 mol%), triphenylacetic acid (2.9 mg, 0.01 mmol, 5 mol%), and Na_2SO_4 (58 mg, 0.4 mmol, 200 mol%) and DCE (1.2 mL) were added to a reaction vessel and then stirred for 30 minutes at room temperature. A solution of 1,6-diyne **4.20** (42mg, 0.2 mmol, 100 mol%) and carbonyl substrate **4.19** (45.6 mg, 0.2 mmol, 100 mol%) in DCE (0.8 mL) was added to a reaction vessel under 1 atm of hydrogen. The mixture was stirred at 45 ^oC under the 1 atm of hydrogen. After 24 hours, a solution of 1,6-diyne **4.19** (42 mg, 0.2mmol, 100 mol%) in DCE (1 mL) was added to a reaction vessel. The mixture was stirred at 45 ^oC under the 1 atm of hydrogen for additional 18 hours. The title compound was purified by flash column chromatography (R_f = 0.2, Hexane/EA = 4/1) to afford 49.8 mg of the coupling product **4.22** as a colorless oil (58 % yield).



4.22

(*Z*)-3-[2-Ethoxycarbonyl-2-hydroxy-2-(4-nitro-phenyl)-ethylidene]-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester1 (4.22). R_f = 0.2, Hexane/EA = 4/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 8.15 – 8.12 (m, 2H), 7.75 – 7.,71 (M, 2h), 6.0 (S, 1h), 5.43 (t, *J* = 2.0 Hz, 1H), 5.04 (s, 1H), 4.26 (s, 1H), 4.22 – 4.10 (m, 2H), 3.17 – 3.06 (m, 2H), 3.04 – 2.89 (m, 2H)1.19 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 173.6, 171.4, 171.3, 148.5, 147.5, 143.5, 140.5, 127.5, 124.0, 123.1, 116.8, 16.5, 63.5, 56.7, 52.9, 52.9, 43.7, 42.1, 13.8. HRMS Calcd. for $C_{14}H_{23}NO_5$ (M+1): 286.1654, Found: 286.1654. FTIR(neat):3447, 2953, 1732, 1669, 1604, 1522, 1435, 1349, 1259, 1200, 1097, 1071, 856.



4.23

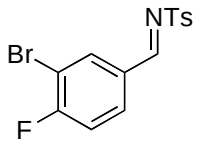
3-[2-Ethoxycarbonyl-2-hydroxy-2-(4-nitro-phenyl)-1-phenyl-ethylidene]-4-methylene-cyclopentane-1,1-dicarboxylic acid dimethyl ester (**4.23**). R_f = 0.2, Hexane/DCM/EA = 12/6/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$ 8.06 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 9.2 Hz, 2H), 7.32 – 7.19 (m, 5H), 5.43 (s, 1H), 4.86 (s, 1H), 4.84 (s, 1H), 3.76 – 3.68 (m, 1H), 3.78 (s, 3H), 3.64 (s, 3H), 3.50 – 3.42 (m, 1H), 2.91 (d, *J* =

16.8 Hz, 1H), 2.87 (d, J = 14.0 Hz, 1H), 2.78 (d, J = 15.6 Hz, 1H), 2.66 (d, J = 16.8 Hz, 1H), 0.85 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 173.3, 172.0, 171.3, 148.3, 147.2, 141.5, 141.0, 140.5, 135.9, 128.8, 128.3, 127.2, 123.0, 122.5, 117.6, 81.1, 63.2, 56.1, 52.9, 52.8, 41.7, 41.4, 13.3. HRMS Calcd. for $C_{14}H_{23}NO_5$ (M+1): 286.1654, Found: 286.1654. FTIR(neat):3467, 2991, 2948, 2949, 2844, 1730, 1596, 1519, 1488, 1437, 1341, 1242, 1203, 1173, 1134, 1078.

4.6.4 Multicomponent Reductive Coupling of Acetylene with Imines

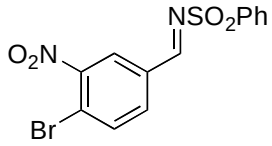
Representative Procedure for Preparation of Aryl Imines

p-Toluenesulfonamide (590 mg, 3.44 mmol, 100 mol%), tetraethyl orthosilicate (717 mg, 3.44 mmol, 100 mol%), and 3-bromo-4-fluorobenzaldehyde (698 mg, 3.44 mmol, 100mol%) were combined in a reaction vessel equipped with short still head and a receiving flask. The reaction mixture was stirred at 165^{o}C for 5 hours, and ethanol, upon formation was collected in the receiving flask. After cooling, the reaction was diluted with ether, suction filtered and filtrates washed with cold ether (3 x 10 mL). The crude compound was recrystallized from EtOAc/hexanes to afford the aldimine in the desired purity.

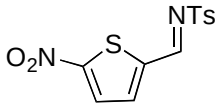


(3-bromo-4-fluorophenyl)-*N*-tosylmethanimine. ^{1}H NMR (400 MHz, $CDCl_3$): 8.94 (s, 1H), 8.18 (d, J = 6.2 Hz, 1H), 7.88 -7.84 (m, 3H) 7.35 (d, J = 8 Hz, 2H), 7.23 (t, J = 8.2

Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.2, 164.2 (d, J_{F-C} = 258.8 Hz), 144.9, 136.0, 134.6, 132.6 (d, J_{F-C} = 8.9 Hz), 129.9 (d, J_{F-C} = 3.7 Hz), 129.9, 128.1, 17.3 (d, J_{F-C} = 23.2 Hz), 110.6 (d, J_{F-C} = 21.7 Hz), 21.6. HRMS Calcd. for $C_{14}H_{12}NO_2FSBr$(M+1): 355.9756, Found: 355.9756. FTIR (neat): 3440, 3210, 1607, 1593, 1491, 1399, 1324, 1260, 1159, 1089, 823, 773, 665 (cm^{-1}). M.P. 126 - 128^{o}C



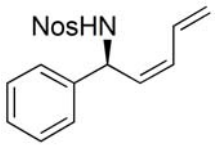
(3-nitro-4-bromophenyl)-*N*-benzensulfonylmethanimine. ^{1}H NMR (400 MHz, $CDCl_3$): 9.03 (s, 1H), 8.35 (s,), 7.99 (d, *J* = 7.8 Hz,), 7.94 – 7.87 (m), 7.67 (t, *J* = 7.6 Hz), 7.57 (t, *J* = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 166.7, 137.1, 136.2, 134.3, 134.2, 132.7, 129.4, 128.3, 126.9, 121.3. HRMS Calcd. for $C_{13}H_{10}N_2O_4S$ Br(M+1): 368.9545, Found: 368.9550. FTIR (neat): 3420, 2945, 1597, 1540, 1320, 1160, 1090, 796 (cm^{-1}). M.P. 159 - 161^{o}C



(5-nitrothiophen-2-yl)-*N*-tosylmethanimine. ^{1}H NMR (400 MHz, $CDCl_3$): 9.05 (s, 1H), 7.90 (d, *J* = 4.3 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 4.3 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 161.6, 145.7, 142.7, 136.1, 134.3, 130.2, 128.6, 128.4, 21.9. HRMS Calcd. for $C_{12}H_{10}N_2O_4S_2$ (M+1): 310.0082, Found: 310.0082. FTIR (neat): 3108, 1596, 1582, 1508, 1344, 1235, 1162, 1087, 821, 760(cm^{-1}). M.P. 196 - 199^{o}C

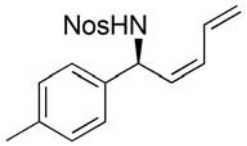
Representative Procedure for Eantioselective Reductive Coupling of Acetylene to *N*-Arylsulfonyl Imine 4.29 for the Coupling Product 4.35

To a reaction vessel charged with $[Rh(COD)_2]BARF$ (11.8 mg, 0.01 mmol, 5 mol%), (S)-Cl,MeO-BIPHEP (6.5 mg, 0.01 mmol, 5 mol%), *m*-nitrobenzoic acid (1.7 mg, 0.01 mmol, 5 mol%), Na_2SO_4 (58 mg, 0.4 mmol, 200 mol%), and imine **4.29** (58 mg, 0.2 mmol, 100 mol%) was added toluene (2.0 mL, 0.1 M). An equimolar mixture of hydrogen and acetylene gas was introduced into the solution *via* cannula. The mixture was stirred at room temperature under the 1 atm of hydrogen and acetylene gas mixture for 16 hours. The title compound was purified by flash column chromatography (Rf = 0.3, Petroleum Ether/$CHCl_3$/EtOAc = 6/3/1) to afford 56.5 mg of the coupling product **4.35** as a yellowish oil (83 % yield).



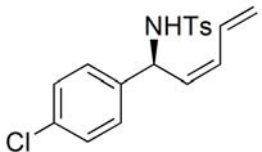
4.32

(Z)-*N*-(4-nitrobenzensulfonyl)-1-phenylpenta-2,4-dien-1-amine (**4.32**). Rf = 0.3, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.17 (d, J = 9 Hz, 2H), 7.84 (d, J = 9 Hz, 2H), 7.21 – 7.16 (m, 5H), 6.59 (dt, J = 16.6 Hz, 10.2 Hz, 1H), 5.98 (t, J = 10.4 Hz, 1H), 5.49 (dd, J = 9.0 Hz, 6.8 Hz, 1H), 5.32 – 5.16 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 146.5, 138.9, 131.9, 130.5, 128.8, 128.5, 128.4, 128.1, 126.7, 123.9, 121.6, 55.1. HRMS Calcd. for $C_{17}H_{17}N_2O_4S$ (M+1): 345.0909, Found: 345.0912. HPLC (Chiralcel OD-H column, 5% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 71.4 min, t_{major} = 76.6 min; ee = 93%. FTIR (neat): 3266, 3102, 2890, 1528, 1432, 1349, 1311, 1164, 1091, 916, 748 (cm^{-1}). M.P. 127 - 128^{o}C



4.33

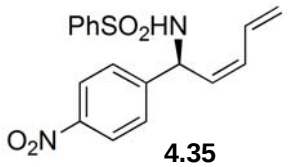
(Z)-*N*-(4-nitrobenzensulfonyl)-1-*p*-tolylpenta-2,4-dien-1-amine (4.33). Rf = 0.4, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (d, *J* = 9 Hz, 2H), 7.84 (d, *J* = 9 Hz, 2H), 7.06 – 6.99 (m, 4H), 6.59 (dt, *J* = 16.6 Hz, 10.2 Hz, 1H), 5.96 (t, *J* = 10.4 Hz, 1H), 5.44 (dd, *J* = 9.4 Hz, 6.6 Hz, 1H), 5.32 – 5.22 (m, 3H), 5.15 (d, *J* = 6.5 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.7, 146.6, 138.1, 136.0, 131.7, 130.6, 129.5, 129.1, 129.0, 128.7, 128.5, 126.7, 123.9, 123.8, 121.4, 54.9, 20.9. HRMS Calcd. for $C_{18}H_{19}N_2O_4S$ (M+1): 359.1066, Found: 359.1071. HPLC (Chiralcel OD-H column, 15% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 22.0 min, t_{major} = 30.1min; ee = 98% FTIR (neat): 3267, 3098, 2982, 1530, 1312, 1164, 1091, 1014, 922, 854, 737 (cm^{-1}). M.P. 98 - 100^{o}C



4.34

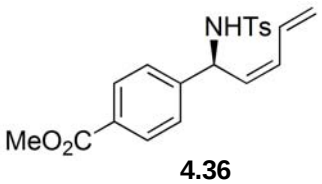
(Z)-*N*-(*p*-tolylsufonyl)-1-(4-chlorophenyl)penta-2,4-dien-1-amine (4.34). Rf = 0.3, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; clear oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.59 (d, *J* = 8.2 Hz, 2H), 7.19 – 7.12 (m, 6H), 6.41 (dt, *J* = 16.4, 10.2 Hz, 1H), 5.95 (t, *J* = 10.2 Hz, 1H), 5.32 -5.13 (m, 4H), 4.95 (d, *J* = 5.8Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 143.5, 138.4, 137.3, 133.5, 131.5, 130.6, 129.4, 128.9, 128.7, 128.1, 127.3, 121.0, 54.2, 21.5. HRMS Calcd. for $C_{18}H_{19}NO_2SCl$ (M+1): 348.0825, Found: 348.0823.

HPLC (Chiralcel OD-H column, 10% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 17.4 min, t_{major} = 23.4 min; ee = 95%. FTIR (neat): 3265, 3029, 2923, 1597, 1491, 1435, 1329, 1160, 1092, 1013, 920, 813, 673 (cm^{-1}).



4.35

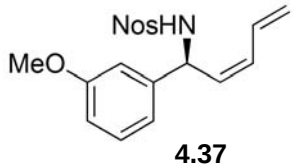
(Z)-*N*-benzensulfonyl-1-(4-nitrophenyl)penta-2,4-dien-1-amine (4.35). Rf = 0.3, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$): 8.06 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.54 – 7.50 (m, 1H), 7.42 – 7.39 (m, 4H), 6.37 (dt, *J* = 16.6 , 10.4 Hz, 1H), 6.02 (t, *J* = 10.6 HZ, 1H), 5.43 (dd, *J* = 9.6, 6.4 Hz, 1H), 5.30 – 5.20 (m, 3H), 5.12 (d, *J* = 6.4Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 147.3, 147.2, 140.0, 132.9, 132.5, 130.1, 129.0, 127.6, 127.5, 127.2, 123.8, 122.1, 54.2. HRMS Calcd. for $C_{17}H_{17}N_2O_4S$ (M+1): 345.0909, Found: 345.0905. HPLC (Chiralcel OD-H column, 20% *i*-PrOH/hexanes, 0.5 mL/min, 254 nm), t_{minor} = 16.8 min, t_{major} = 27.0 min; ee = 97% FTIR (neat): 3276, 3067, 2906, 1599, 1520, 1448, 1347, 1161, 1092, 923, 853 (cm^{-1}).



4.36

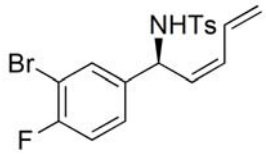
Methyl 4-((Z)-*N*-(*p*-tolylsulfonyl)-1-aminopenta-2,4-dienyl)benzoate (4.36). Rf = 0.2, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; clear oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, *J*

= 8.2 Hz, 2H), 7.60 (d, *J* = 8.2Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.43 (dt, *J* = 16.8, 10.2 Hz, 1H), 5.98 (t, *J* = 10.6 Hz, 1H), 5.38 (dd, *J* = 9.6, 6.2 Hz, 1H), 5.30 – 5.17 (m, 3H), 4.97 (d, *J* = 6.2 Hz, 1H), 3.88 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 166.6, 144.9, 143.5, 137.3, 131.9, 130.6, 129.9, 129.5, 128.7, 127.3, 126.7, 121.3, 54.6, 52.1, 21.5. HRMS Calcd. for $C_{20}H_{22}NO_4S$ (M+1): 372.1270, Found: 372.1268. HPLC (Chiralcel OD-H column, 10% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 26.8 min, t_{major} = 35.3 min; ee = 95% FTIR (neat): 3270, 2994, 1770, 1720, 1610, 1436, 1374, 1280, 1245, 1160, 1060, 913 (cm^{-1}).



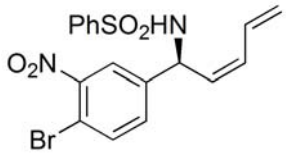
4.37

(Z)-*N*-(4-nitrobenzensulfonyl)-1-(3-methoxyphenyl)penta-2,4-dien-1-amine (4.37). Rf = 0.3, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; yellowish solid; ^{1}H NMR (400 MHz, $CDCl_3$): 8.16 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 9.0 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.76 – 6.53 (m, 4H), 5.98 (t, *J* = 10.6 Hz, 1H), 5.44 (dd, *J* = 9.4, 6.6 Hz, 1H), 5.30 – 5.19 (m, 4H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 159.84, 149.7, 146.5, 140.5, 131.9, 130.5, 129.9, 128.4, 128.4, 123.8, 121.6, 118.9, 112.9, 112.7, 55.2, 55.0. HRMS Calcd. for $C_{18}H_{19}N_2O_5S$ (M+1): 375.1015, Found: 375.1016. HPLC (Chiralcel AD-H column, 15% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{major} = 47.1 min, t_{minor} = 75.9 min; ee = 97% FTIR (neat): 3266.79, 2878.5, 2330.9, 1603.6, 1528.8, 1431.6, 1344.2, 1311.9, 1263.27, 1160.5, 1091.3, 1042.0, 910.0, 853.3, 734.7 (cm^{-1}). M.P. 104 – 105^{o}C



4.38

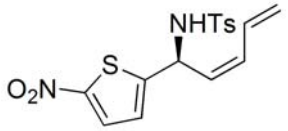
(Z)-*N*-(*p*-tolylsulfonyl)-1-(3-bromo-fluorophenyl)penta-2,4-dien-1-amine (4.38). Rf = 0.2, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; clear oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.57 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 6.5 Hz, 1H), 7.18 (d, J = 8.2 Hz, 2H), 7.16 – 7.12 (m, 1H), 6.95 (t, J = 8.2 Hz, 1H), 6.41 (dt, J = 16.6, 10.2 Hz, 1H), 5.98 (t, J = 10.2 Hz, 1H), 5.31 – 5.18 (m, 4H), 4.98 (d, J = 6.2 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 158.4 (d, $J_{F\text{-}C}$ = 247 Hz), 143.7, 137.3 (d, $J_{F\text{-}C}$ = 3.7 Hz), 137.1, 131.9 (d, $J_{F\text{-}C}$ = 6.7 Hz), 130.5, 129.5, 128.4, 127.5 (d, $J_{F\text{-}C}$ = 7.5 Hz), 127.2, 121.5, 116.4 (d, $J_{F\text{-}C}$ = 22.4 Hz), 109.1 (d, $J_{F\text{-}C}$ = 21.7 Hz), 53.7, 21.5. HRMS Calcd. for $C_{18}H_{18}NO_2FSBr$ (M+1): 410.0026, Found: 410.0230. HPLC (Chiralcel OD-H column, 5% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 28.6 min, t_{major} = 36.6 min; ee = 97% FTIR (neat): 3265, 2970, 2923, 1597, 1494, 1436, 1329, 1246, 1160, 1093, 1047, 921, 813 (cm^{-1}).



4.39

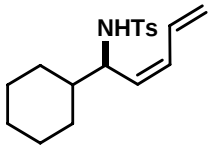
(Z)-*N*-(benzensulfonyl)-1-(4-bromo-3-nitrophenyl)penta-2,4-dien-amine (4.39). Rf = 0.3, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 7.2 Hz, 2H), 7.62 – 7.51(m, 3H), 7.41 (t, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 1H), 6.34 (dt, J = 16.6, 10.8 Hz, 1H), 6.04 (t, J = 10.2 Hz, 1H), 5.39 – 5.19 (m, 4H), 5.04

(d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.9, 141.6, 140.1, 135.5, 133.2, 133.2 131.9, 130.2, 129.3, 127.4, 127.1, 124.2, 122.8, 113.8, 53.9. HRMS Calcd. for $C_{17}H_{16}N_2O_4SBr$ (M+1): 423.0014, Found: 423.0014. HPLC (Chiralcel OD-H column, 20% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 15.2 min, t_{major} = 22.4 min; ee = 94%. FTIR (neat): 3320, 3210, 2946, 1538, 1473, 1448, 1332, 1162, 1092, 1032, 922 (cm^{-1}).



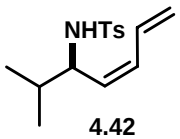
4.40

(Z)-*N*-(*p*-tolylsulfonyl)-1-(5-nitrothiophen-2-yl)penta-2,4-dien-1-amine (4.40). Rf = 0.2, petroleum ether/$CHCl_3$/EtOAc = 6/3/1; a brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 – 7.62 (m, 3H), 7.24 (d, J = 10.8 Hz, 2H), 6.83 (d, J = 4.1 Hz, 1H), 6.32 (dt, J = 16.6, 9.8 Hz, 1H), 6.04 (t, J = 10.8Hz, 1H), 5.57 – 5.45 (m, 1H), 5.32 – 5.13(m, 4H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 153.3, 151.1, 144.2, 136.8, 133.2, 129.8, 129.7, 128.5, 127.2, 126.3, 124.4, 122.5, 51.0, 21.5. HRMS Calcd. for $C_{16}H_{17}N_2O_4S_2$ (M+1): 365.0630, Found: 365.0629. HPLC (Chiralcel OD-H column, 15% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 21.2 min, t_{major} = 37.1 min; ee = 95% FTIR (neat): 3260, 3106, 2924, 1597, 1503, 1434, 1337, 1161, 1092, 922, 815, 734, 675 (cm^{-1}).



4.41

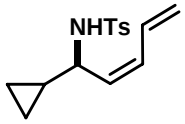
(Z)-N-(1-Cyclohexyl-penta-2,4-dienyl)-4-methyl-benzenesulfonamide (4.41). Rf = 0.3, hexane/$CHCl_3$/EtOAc = 8/3/1); white solid; ^{1}H NMR (300 MHz, $CDCl_3$): 7.66 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.33 (dt, *J* = 16.5 Hz, 10.7 Hz, 1H), 5.80 (t, *J* = 10.9 Hz, 1H), 5.10 (d, *J* = 16.5 Hz, 1H), 5.05 (d, *J* = 11.1 Hz, 1H), 4.96 (t, *J* = 10.4 Hz, 1H), 4.73 (d, *J* = 8.1 Hz, 1H), 3.97 (dd, *J* = 17.1, 7.5 Hz, 1H), 2.36 (s, 3H), 1.79 – 1.59 (m, 5H), 1.42 – 1.30 (m, 1H), 1.23 – 1.03 (m, 3H), 0.96 – 0.84 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 142.9, 138.0, 131.4, 131.0, 129.4, 129.3, 127.2, 119.1, 55.9, 43.0, 29.1, 28.5, 26.2, 25,9, 25.8, 21.4. HRMS Calcd. for $C_{18}H_{26}NO_2S$ (M+1): 320.1684, Found: 320.1687. FTIR(neat): 3273, 2925, 2852, 1652, 1598, 1558, 1540, 1506, 1448, 1327, 1158, 1093, 1042, 905, 812, 674 (cm^{-1}). HPLC (Chiralcel OD-H column, 5% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 16.7 min, t_{major} = 21.8 min; ee = 97% MP : 113 - 114 ^oC



4.42

(Z)- N-(1-Isopropyl-penta-2,4-dienyl)-4-methyl-benzenesulfonamide (4.42). Rf = 0.3, hexane/$CHCl_3$/EtOAc = 8/3/1; white solid; ^{1}H NMR (400 MHz, $CDCl_3$): 7.68 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.35 (dtd, *J* = 16.8 Hz, 10.6, 0.4 Hz, 1H), 5.85 (t, *J* = 10.8 Hz, 1H), 5.14 (d, *J* = 16.8 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.99 (t, *J* = 10.4 Hz,

1H), 4.60 (d, J = 8.0 Hz, 1H), 4.02 – 3.96 (m, 1H), 2.39 (s, 3H), 1.79 – 1.70 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.4, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 142.9, 137.9, 131.3, 131.3, 129.3, 128.9, 127.2, 119.2, 56.5, 33.4, 21.4, 18.5, 17.9. HRMS Calcd. for $C_{15}H_{22}NO_2S$ (M+1): 280.1371, Found: 280.1374. FTIR(neat): 3273, 2962,2927, 2874, 1916, 1802, 1647, 1598, 1495, 1434, 1328, 1304, 1158, 1093, 1047, 915, 813, 788, 706, 676 (cm^{-1}). HPLC (Chiralcel OD-H column, 5% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 18.1 min, t_{major} = 20.6 min; ee = 98% MP : 71 - 72 ^{o}C



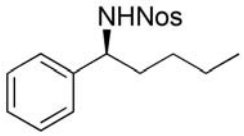
4.43

(Z)- N-(1-Cyclopropyl-penta-2,4-dienyl)-4-methyl-benzenesulfonamide (4.43). Rf = 0.3, hexane/$CHCl_3$/EtOAc = 8/3/1); clear oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (dd, J = 6.5, 1.7 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 6.41 (dtd, J = 17.1 Hz, 10.2, 0.9 Hz, 1H), 5.91 (td, J = 11.1, 0.9 Hz, 1H), 5.22 (d, J = 16.5 Hz, 1H), 5.15 (d, J = 9.9 Hz, 1H), 5.08 (t, J = 10.5 Hz, 1H), 4.61 (s, br, 1H), 3.82 – 3.74 (m, 1H), 2.43 (s, 3H), 1.00 – 0.89 (m, 1H), 0.50 – 0.43 (m, 2H), 0.27 – 0.21 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 143.2, 137.9, 131.2, 130.9, 129.4, 129.2, 127.3, 119.7, 55.0, 21.5, 16.6, 3.5, 2.5. HRMS Calcd. for $C_{15}H_{20}NO_2S$ (M+1): 278.1215, Found: 278.1215. FTIR(neat): 3265, 3078, 3008, 2918, 2848, 1598, 1431, 1325, 1157, 1093, 1028, 911, 813 (cm^{-1}). HPLC (Chiralcel OD-H column, 5% *i*-PrOH/hexanes, 0.5 mL/min, 220 nm), t_{minor} = 24.5 min, t_{major} = 27.7 min; ee = 97%

Determination of Absolute Stereochemistyry

Procedure for the Exhaustive Hydrogenation of 4.32

To the solution of diene **4.32**(40 mg, 0.174 mmol, 100 mol%) in DCM (1.2 mL, 0.1 M) at ambient temperature was added Crabtree's catalyst (7.0 mg, 0.0087 mmol, 5 mmol). The reaction was purged with argon followed by hydrogen. The reaction was allowed to stir at ambient temperature under 1 atm of hydrogen for 30h. The volatiles were removed under reduced pressure. The title compound was purified by silica gel flash chromatography (Rf = 0.4: 60/30/10 Petroleum Ether/$CHCl_3$/EtOAc) to afford to afford 39.9 mg of **4.44** as a clear oil (99 % yield).

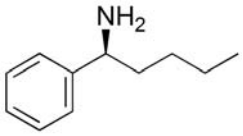


4.44

***(S)*-*N*-(4-nitrobezylsufonyl)-1-phenylpentan-1-amine (4.44).** ^{1}H NMR (400 MHz, $CDCl_3$): 8.04 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.11 – 7.05 (m, 3H), 6.92 (d, *J* =7.5 Hz, 2H), 5.02 (d, *J* = 7.2 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 1H), 1.82 – 1.61 (m, 2H), 1.30 – 1.09 (m, 4H), 0.82 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 146.6, 140.0, 128.5, 128.1, 127.8, 126.5, 123.7, 58.8, 37.3, 27.9, 22.1, 13.8. FTIR (neat): 3280, 2932, 2874, 1529, 1456, 1349, 1164, 1092, 913, 744 (cm^{-1}). HRMS Calcd. For $C_{17}H_{21}N_2O_4S$ (M+1): 349.1222, Found: 349.1223.

Procedure for the Deprotecton of *p*-Nitrobenzenesulforyl Group

A mixture of compound **4.44** (74 mg, 0.212 mmol, 100 mol%), PhSH (0.087 mL, 0.848 mmol, 400 mol%), and K_2CO_3 (176 mg, 1.272 mmol, 600 mol%) were dissolved in MeCN (2.12 mL, 0.1M). The reaction mixture was stirred at 50°C for 24 h under argon pressure. The title compound was purified by silica gel flash chromatography (Rf = 0.05: 50/50/1 Petroleum Ether/EtOAc/TEA) to afford to afford 22.6 mg of **4.45** as a clear oil (66 % yield).



4.45

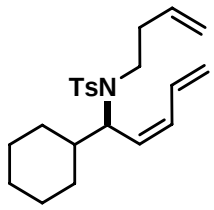
(*S*)-1-phenylpentan-1-amine (**4.45**)**.** ^{1}H NMR (400 MHz, $CDCl_3$): 7.33 – 7.20 (m, 5H), 3.85 (t, *J* = 6.8 Hz, 1H), 1.67 – 1.30 (m, 4H), 1.29 – 1.17 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H). $[\alpha]_D$ = -17.2 (c = 0.67, DCM, 94% ee) compared to $[\alpha]_D$ = -17.4 (1.19, DCM, 94 % ee).

Elaboration of the Redcutive Coupling Product

Procedure for *N*-Homoallylation of 4.41.

Amine **4.41** (34.2 mg, 0.108 mmol, 100 mol%), Cs_2CO_3 (176.2 mg, 1.08 mmol, 10 eq.), and homoallyl bromide (73.0 mg, 1.08 mmol, 10 eq.) were suspended in 0.35 mL of DMF and the mixture stirred overnight at 70 °C. Water and ether were added to the suspension, and the aqueous layer was extracted three times with ether. The combined

organic layers were dried with Na_2SO_4. After filtration and concentration under low pressure. The residue was purified by flash column chromatography (Rf = 0.4, Hexane /EtOAc = 10/1) to afford 28.9 mg as a clear oil (84 % yield).



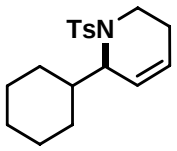
4.46

(Z)-*N*-But-3-enyl-N-(1-cyclohexyl-penta-2,4-dienyl)-4-methyl-benzenesulfonamide (**4.46**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.60 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.64 (dt, *J* = 16.8 Hz, 10.2 Hz, 1H), 6.00 (t, *J* = 11.1 Hz, 1H), 5.73 – 5.60 (m, 1H), 5.25 – 5.17 9m, 3H), 5.04 – 4.97 (m, 2H), 4.52 (t, *J* = 10.5 Hz, 1H), 3.16 – 2.95 (m, 2H), 2.49 – 2.39 (m, 1H), 2.35 (s, 3H), 2.30 – 2.18 (m, 1H), 2.01 (d, *J* = 12.6 Hz, 1H), 1.76 – 1.62 (m, 4H), 1.44 – 1.33 (m, 1H), 1.23 – 0.99 (m, 4H), 0.90 – 0.77 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 142.7, 137.7, 135.0, 132.5, 132.0, 129.2, 127.5, 127.2, 119.7, 116.7, 60.5, 43.8, 40.3, 35.1, 30.5, 30.2, 26.3, 26.1, 25.9, 21.5. HRMS Calcd. for $C_{22}H_{32}NO_2S$ (M+1): 374.2154, Found: 374.2151. FTIR(neat): 2924, 2851, 1641, 1598, 1450, 1337, 1154, 1090, 917, 812, 750, 663 (cm^{-1}).

Procedure for Ring-Closing Metathesis of 4.46.

The triene **4.46** (17.6 mg, 0.047 mmol, 100 m0l%) was dissolved in dry degassed DCM (0.5 mL, 0.1M) in a round-bottom flask under argon. The Grubbs catalyst (2.0 mg, 0.0024 mmol, 5 mol%) was added, and the solution was stirred at reflux until the starting

material was totally consumed. The solvent was evaporated, and the crude was purified by flash column chromatography (Rf = 0.4, Hexane /EtOAc = 10/1) to afford 14.3 mg of **4.47** as a clear oil (95 % yield).

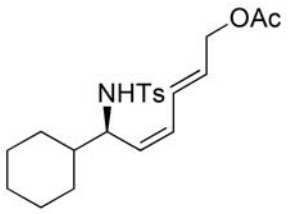


4.47

6-Cyclohexyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine (**4.47**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.67 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 5.73 -5.69 (m, 1H), 5.53 (d, *J* = 10.8 Hz, 1H), 3.98 (s, br, 1H), 3.84 – 3.79 (m, 1H), 3.17 – 3.09 (m, 1H), 1.92 (d, *J* = 12.8 Hz, 1H), 1.75 – 1.47 (m, 6H), 1.23 – 1.01 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 142.8, 138.8, 129.4, 127.1, 126.2, 125.1, 58.3, 43.1, 39.1, 30.2, 29.8, 26.3, 26.2, 26.1, 22.4, 21.5. HRMS Calcd. for $C_{18}H_{26}NO_2S$ (M+1): 320.1684, Found: 320.1688. FTIR(neat): 3036, 2924, 2851, 1598, 1494, 1449, 1342, 1283, 1212, 1159, 1059, 1041, 963, 925, 814, 717, 649 (cm^{-1}).

Procedure for Cross Metathesis of 4.41.

Amine **4.41** (25 mg, 0.078 mmol) was dissolved in anhydrous DCM (0.4 mL) and 1,4-acetate-2-butene (40 mg, 0.234 mmol) was added, following Grubb's II (3.3 mg, 0.0039 mmol). The reaction mixture was stirred for 14 hours. The title compound was purified by flash column chromatography (Rf = 0.2, Petroleum Ether/$CHCl_3$/EtOAc = 6/3/1) to afford 22 mg (6:1 E:Z) as a clear oil (72 % yield).

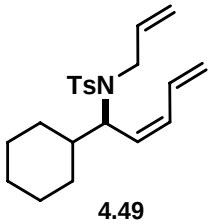


4.48

(*2E,4Z*)-6-*N*-*p*-tolylsulfonyl-amino-6-cyclohexylhexa-2,4-dienyl acetate (4.48). ^{1}H NMR (400 MHz, $CDCl_3$): 7.64 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.24 (dd. *J* = 15.0, 11.2 Hz, 1H) 5.82 (t, *J* = 10.9 Hz, 1H), 5.64 (dt, *J* = 15.0, 6.5 Hz, 1H), 5.02 (t, *J* = 10.6 Hz, 1H), 4.53 (d, *J* = 6.5 Hz, 1H), 4.65 (d, *J* = 7.8 Hz, 2H), 3.94 (dt, *J* = 10.2, 7.2 Hz, 1H), 2.37 (s, 3H), 2.08 (s, 3H), 1.77 – 1.59 (m, 5H), 1.39 – 1.32 (m, 1H), 1.17 – 1.04 (m, 3H), 0.95 – 0.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.7, 143.1, 137.9, 130.1, 129.6, 129.4, 128.8, 128.2, 127.2, 64.5, 55.9, 42.9, 29.1, 28.5, 26.2, 25.9, 25.8, 21.5, 20.9. HRMS Calcd. for $C_{21}H_{30}NO_4S$ (M+1): 392.1896, Found: 392.1891. FTIR (neat): 3270, 2926, 2852, 1740, 1598, 1448, 1330, 1240, 1160, 1093, 1027, 956, 814 (cm^{-1}).

Procedure for *N*-Allylation of 4.41.

Amine **4.41** (104.3 mg, 0.33 mmol, 100 mol%), K_2CO_3 (68.4 mg, 0.49 mmol, 150 mol%.), and allyl bromide (60.0 mg, 0.49 mmol, 150 mol%).) were suspended in 1.1 mL of DMF and the mixture stirred overnight at room temperature. Water and ether were added to the suspension, and the aqueous layer was extracted three times with ether. The combined organic layers were dried with Na_2SO_4, and the solvent was removed under low pressure. The residue was purified by flash column chromatography (Rf = 0.4, Hexane /EtOAc = 10/1) to afford 118.6 mg as a clear oil (100 % yield).



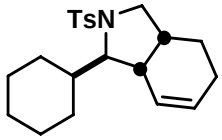
4.49

(Z)-N-Allyl-N-(1-cyclohexyl-penta-2,4-dienyl)-4-methyl-benzenesulfonamide (**4.49**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.60 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.65 (dt, *J* = 16.8 Hz, 10.8 Hz, 1H), 6.00 (t, *J* = 11.2 Hz, 1H), 5.80 – 5.70 (m, 1H), 5.28 (t, *J* = 11.0 Hz, 1H), 5.22 (dt, *J* = 16.4 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 5.10 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.01 (dd, *J* = 9.8, 1.4 Hz, 1H), 4.53 (t, *J* = 10.6 Hz, 1H), 3.75 (dd, *J* = 16.4, 7.4 Hz, 1H), 3.66 (ddt, *J* = 16.2, 5.8, 1.4 Hz, 1H), 1.96 (d, *J* = 12.8 Hz, 1H), 1.74 – 1.56 (m, 4H), 1.50 – 1.40 (m, 1H), 1.23 – 0.93 (m, 4H), 0.85 – 0.71 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 142.7, 137.7, 135.8, 132.2, 131.9,, 129.1, 127.8, 127.5, 119.5, 117.0, 60.3, 47.0, 39.6, 30.1, 26.2, 26.0, 25.7, 21.4. HRMS Calcd. for $C_{21}H_{30}NO_2S$ (M+1): 360.1997, Found: 360.1995. FTIR(neat): 2923, 2852, 1738, 1593, 1492, 1449, 1337, 1262, 1155, 1090, 1037, 1007, 921, 812, 767, 662 (cm^{-1}).

Procedure for Rh-Catalyzed [4+2] Cycloaddition of 4.49

A flame-dried 10 mL Schlenk tube was charged with $[Rh(COD)_2]SbF_6$ (3.1 mg, 0.0057 mmol, 5 mol%) and PPh_3 (4.5 mg, 0.017 mmol, 15 mol%), and fitted with a rubber septum. The flask was evacuated under high vacuum and back filled with argon. The precatalyst was dissolved in toluene (0.6 mL), allowed to stir for 5 min, then purged with H_2 and rapidly stirred for an additional 30 min. The H_2 was removed and followed by back filling with argon. The triene **4.49** (40.7 mg, 0.113 mmol, 100 mol%) in toluene

(0.6 mL) was then added by syringe and the reaction mixture was warmed to 80 ^{o}C with stirring 20 min. After the cycloaddition was complete (TLC), the solvent was evaporated, and the crude was purified by flash column chromatography (Rf = 0.4, Hexane /EtOAc = 10/1) to afford 35.5 mg as a clear oil (87 % yield, 9:1 dr).

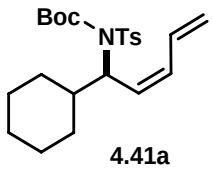


4.50

1-Cyclohexyl-2-(toluene-4-sulfonyl)-2,3,3a,4,5,7a-hexahydro-1H-isoindole (4.50). (Note: The ratio of two diastereomers was determined by HPLC using the reacemic product. In addition, the relative stereochemistry of the major diastereomer was assigned based on the report by Livinghouse). ^{1}H NMR (400 MHz, $CDCl_3$): 7.65 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.10 -5.08 (m, 1H), 4.93 (d, *J* = 10.4 Hz, 1H), 3.36 (dd, *J* = 9.6, 7.6 Hz, 1 H), 3.20 (d, *J* = 3.6 Hz, 1H), 3.01 (t, *J* = 9.0 Hz, 1H), 2.45 – 2.43 (m, 2H), 1.81 – 1.56 (m, 7H), 1.51 – 1.34 (m, 2H), 1.31 -1 0.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 142.8, 138.8, 129.1, 128.1, 127.7, 126.5, 71.3, 50.5, 43.0, 39.6, 34.8, 30.4, 28.0, 26.6, 26.4, 26.2, 21.5, 20.9, 20.2. HRMS Calcd. for $C_{21}H_{30}NO_2S$ (M+1): 360.1997, Found: 360.1995. FTIR(neat): 3018, 2928, 2848, 1598, 1449, 1342, 1304, 1160, 1405, 1090, 1032, 988, 915, 846, 814, 709, 665 (cm^{-1}).

Procedure for Boc-Protection of 4.41

A solution of amine (61.0 mg, 0.19 mmol, 100 mol%) and Boc_2O (52.0 mg, 0.23 mmol, 120 mol%) in MeCN (1 mL, 0.2M) was treated with DMAP (2.4 mg, 0.019 mmol, 10 mol%) and left overnight under argon. Water and ether were added to the suspension, and the aqueous layer was extracted three times with ether. The combined organic layers were dried with Na_2SO_4, and the solvent was removed under low pressure. The residue was purified by flash column chromatography (Rf = 0.4, Hexane /EtOAc = 10/1) to afford 81.0 mg as a clear oil (100 % yield).

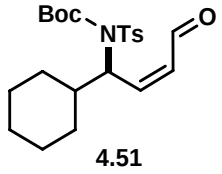


4.41a

N-*tert*-Butoxycarbonyl-N(1-Cyclohexyl-penta-2,4-dienyl)-4-methyl-benzenesulfon-amide (**4.41a**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.67 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.85 (dt, *J* = 16.8 Hz, 10.6 Hz, 1H), 6.23 (t, *J* = 10.9 Hz, 1H), 5.86 (t, *J* = 10.4 Hz, 1H), 5.32 (d, *J* = 16.5 Hz, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 5.08 (t, *J* = 10.1 Hz, 1H), 2.38 (s, 3H), 2.11 -2.00 (m, 1H), 1.90 – 1.78 (m, 2H), 1.72 – 1.63 (m, 3H), 1.28 (s, 9H), 1.37 – 1.00 (m, 4H), 0.89 – 0.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 150.6, 143.5, 137.8, 133.2, 132.1, 129.2, 129.0, 127.7, 120.0, 84.0, 60.7, 39.5, 31.1, 29.8, 27.9, 26.2, 25.9, 25.8, 21.5. HRMS Calcd. for $C_{23}H_{34}NO_4S$ (M+1): 420.2209, Found: 420.2206. FTIR(neat): 2929, 1724, 1597, 1495, 1450, 1393, 1355, 1278, 1256, 1162, 1087, 991, 813, 706, 665 (cm^{-1}).

Procedure for Site-Selective Oxidative Cleavage of 4.41a

To a mixture of 1.2 mL of water and 2.9 mL of THF, OsO_4 (2.5 mg, 0.01 mmol, 5 mol%) and diene **4.41a** (85.2 mg, 0.20 mmol, 100 mol%) was added and then stirred for 5 minutes. While the temperature of the stirred mixture was maintained at 24 – 26 °C, $NaIO_4$ (95.5 mg, 0.45 mmol, 220 mol%) was added in portions over a period of 40 minutes. The solution was stirred for an additional 2 hours. The mixture was extracted thoroughly with ether and the combined organic layers were dried with Na_2SO_4. The solvent was removed *in vacuo*, and then the title compound was purified by flash silical chromatography (Rf = 0.4, EtOAc/hexane = 1/6) to afford 70.3 mg as a colorless oil (83% yield).

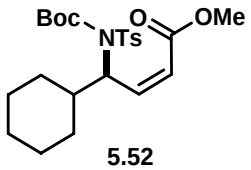


4.51

N-*tert*-Butoxycarbonyl-N-(1-Cyclohexyl-4-oxo-but-2-enyl)-4-methyl-benzenesulfon-amide (**4.51**). ^{1}H NMR (300 MHz, $CDCl_3$): 10.2 (d, J = 8.1 Hz), 7.69 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 7.5 Hz, 2H), 7.04 (t, J = 10.9 Hz, 1H), 6.18 (dd, J = 10.8, 8.1 Hz, 1H), 5.54 (t, J = 10.5 Hz, 1H), 2.25 (m, 1H)- 2.06 (s, 3H), 1.89 – 1.65 (m, 5H), 1.34 (s, 9H), 1.30 – 0.88 9m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.3, 150.3, 147.2, 144.3, 137.0, 132.4, 129.3, 127.9, 85.0, 59.3, 38.5, 31.3, 29.6, 27.8, 26.0, 25.7, 25.6, 21.6. HRMS Calcd. for $C_{22}H_{32}NO_5S$ (M+1): 422.2001, Found: 422.2004. FTIR(neat):2930, 2853, 1725, 1683, 1597, 1450, 1348, 1281, 1150, 1087, 1022, 943, 812, 768, 665 (cm^{-1}).

Procedure for Oxidation of 4.51

To a solution of aldehyde **4.51** (31.8 mg, 0.075 mmol, 100 mol%) in MeOH (1.4 mL, 0.05M) was added manganese dioxide (154 mg, 1.5 mmol, 20 eq.) and sodium cyanide (15.5 mg, 0.30 mmol, 400 mol%). The resulting suspension was stirred at room temperature for 3 hrs, filtered and the filtrate evaporated. The residue was redissolved in water and extracted with ether, the combined organic extracts were dried with Na2SO4 and evaporated. The residue was purified by flash silical chromatography (Rf = 0.4, EtOAc/hexane = 1/6) to afford 26.3 mg as a colorless oil (77% yield).



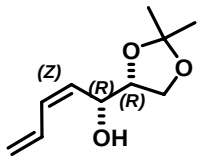
5.52

N-*tert*-Butoxycarbonyl-N-4-Cyclohexyl-4-(toluene-4-sulfonylamino)-but-2-enoic acid methyl ester (**5.52**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.75 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.63 (dd, *J* = 11.9, 10.0 Hz, 1H), 6.00 (dd, *J* = 11.7, 0.6 Hz, 1H), 5.92 (t, *J* = 10.2 Hz, 1H), 3.78 (s, 3H), 2.43 (s, 3H), 2.14 – 2.03 (m, 1H), 1.84 – 1.64 (m, 5H), 1.37 (s, 9H), 1.34 – 1.04 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.0, 150.8, 144.1, 143.7, 137.3, 129.0, 127.9, 122.5, 84.3, 60.0, 51.5, 39.4, 30.3, 29.7, 27.9, 26.1, 26.0, 26.0, 21.5. HRMS Calcd. for $C_{23}H_{34}NO_6S$ (M+1): 452.2107, Found: 452.2110. FTIR(neat): 2930, 2852, 1726, 1648, 1598, 1450, 1357, 1277, 1167, 1152, 1087, 988, 814, 668 (cm^{-1}).

4.6.5 Reductive Coupling of Acetylene with Chiral Aldehydes: The Formal Synthesis of D-Hexoses

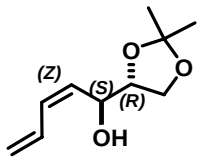
Representative Procedure for Diastereoselective Reducitve Coupling

$[Rh(COD)_2]BARF$ (11.8mg, 0.01 mmol, 5 mol%), (R)-MeO-BIPHEP (5.9mg, 0.01 mmol, 5 mol%), petafluorobenzoic acid (2.1mg, 0.01 mmol, 5 mol%), and Na_2SO_4 (58mg, 0.4 mmol, 200 mol%) and Toluene (1.2 mL) were added to a reaction vessel and then stirred for 15 minutes at room temperature. The mixture of hydrogen and acetylene gas (approximately 1:1 mixture) was introduced into the solution *via* cannula and then a solution of carbonyl substrate **4.57** (26mg, 0.2 mmol, 100 mol%) in Toluene (0.8 mL) was added to a reaction vessel. The mixture was stirred at room temperature under the 1 atm of hydrogen and acetylene gas mixture for 12 hours. The title compound was purified by flash column chromatography (R_f = 0.3, pentane/ether = 2/1) to afford 28.7 mg of ***syn*-4.58** as a colorless oil (78 % yield, >20:1 dr).



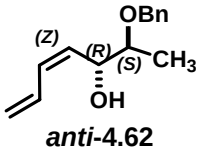
***syn*-4.58**

(*Z,1R*)-1-((*4R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-penta-2,4-dien-1-ol (*syn*-4.58). R_f = 0.3, Pentane/Ether = 2/1; colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 6.70 – 6.63 (m, 1H), 6.16 (td, *J* = 11.2, 0.8 Hz, 1H), 5.37 – 5.21 (m, 3H), 4.47 (t, *J* = 8.0 Hz, 1H), 4.04 – 4.00 (m, 1H), 3.95 (d, *J* = 6.4 Hz, 1H), 3.93 (d, *J* = 6.4 Hz, 1H), 3.68 (dd, *J* = 5.6, 5.4 Hz, 1H), 2.39 (s, br, 1H), 1.45 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 133.4, 131.5, 128.4, 120.6, 109.9, 79.1, 69.2, 65.7, 26.9, 25.2. HRMS Calcd. for $C_{10}H_{17}O_3$ (M+1): 185.1178, Found: 185.1182.



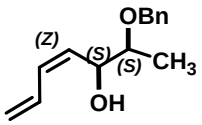
***anti*-4.58**

***Z,1S*)-1-((*4R*)-2,2-Dimethyl-[1,3]dioxolan-4-yl)-penta-*Z*-2,4-dien-1-ol (*anti*-4.58).** R_f = 0.3, Pentane/Ether = 2/1; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 6.62 (dtd, *J* = 16.4, 10.6, 1.2 Hz, 1H), 6.16 (td, *J* = 11.2, 0.7 Hz, 1H), 5.34 (t, *J* = 9.8 Hz, 1H), 5.28 (dd, *J* = 16.8, 0.2 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 4.73 – 4.71 (m, 1H), 4.10 (td, *J* = 6.6, 4.4 Hz, 2H), 3.98(dd, *J* = 8.2, 6.8 Hz, 1H), 3.92 (dd, *J* = 8.4, 6.8 Hz, 1H), 2.08 (d, *J* = 2.8 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 133.0, 131.5, 128.5, 120.3, 109.4, 78.1, 67.5, 64.7, 26.4, 25.1. HRMS Calcd. for $C_{10}H_{17}O_3$ (M+1): 185.1178, Found: 185.1176.



***anti*-4.62**

(*Z,2S,3R)*-2-Benzyloxy-hepta-4,6-dien-3-ol (*anti*-4.62). R_f = 0.3, Hexane/EA = 8/1; o afford 41.6 mg as a colorless oil (95 % yield, 11:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 – 7.24 (m, 5H), 6.61 – 6.51 (m, 1H), 6.12 (t, *J* = 11.0 Hz, 1H), 5.46 (t, *J* = 9.4 Hz, 1H), 5.25 (dt, *J* = 16.8, 0.8 Hz, 1H), 5.16 (d, *J* = 10.4 Hz, 1H), 4.68 – 4.64 (m, 1H), 4.64 (dt, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 3.64 – 3.59 (m, 1H), 2.31 (d, *J* = 4.4 Hz, 1H), 1.14 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 138.4, 131.8, 131.7, 129.8, 128.4, 127.7, 127.6, 119.4, 77.6, 70.9, 69.9, 14.1. HRMS Calcd. for $C_{14}H_{19}O_2$ (M+1): 219.1385, Found: 219.1384.

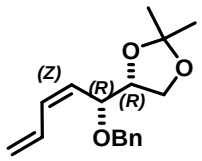


***syn*-4.62**

(*Z,2S,3S*)-2-Benzyloxy-hepta-4,6-dien-3-ol (*syn*-4.62). R_f = 0.3, Hexane/EA = 8/1; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): 7.38 – 7.26 (m, 5H), 6.65 (dtd, *J* = 16.5,10.7, 1.2 Hz, 1H), 6.17 (t, *J* = 11.2 Hz, 1H), 5.38 (t, *J* = 10.0 Hz, 1H), 5.27 (dd, *J* = 16.5, 1.7 Hz, 1H), 5.19 (d, *J* = 11.4 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.40 (t, *J* = 8.2 Hz, 1H), 3.47 – 3.39 (m, 1H), 2.38 (d, *J* = 2.1 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.1, 133.2, 132.0, 129.6, 128.54, 127.8, 119.7, 78.6, 71.5, 71.2, 15.4. HRMS Calcd. for $C_{14}H_{19}O_2$ (M+1): 219.1385, Found: 219.1384.

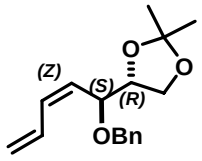
Representative Procedure for Benzylation of the Coupling Product.

NaH (17.2mg, 130 mol%) was added to a solution of diene product **syn-4.58** (61mg, 100 mol%) in anhydrous DMF (2.0mL, 0.12M) at 0 ^{o}C under argon atmosphere. After 10 min benzyl bromide (78.9mg, 137 mol% in DMF (0.75mL)) was added in one portion. The reaction mixture was stirred for 2h, and then carefully quenched with saturated NH_4Cl. The mixture was extracted with ether. The combined organic phase washed with water and brine, and dried with $MgSO_4$. After filtration and evaporation under reduced pressure. The title compound was purified by flash column chromatography (R_f = 0.3, Hexane/EA = 10/1) to afford 80.7 mg as a colorless oil (89 % yield).



4.69

(*Z,4R*)-4-((*1R*)-1-Benzyloxy-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolane (4.69). R_f = 0.3, Hexane/EA = 10/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 – 7.24 (m, 5H), 6.50 (dtd, *J* = 16.8, 10.0, 0.8 Hz, 1H), 6.31 (td, *J* = 11.2, 0.4 Hz, 1H), 5.36 – 5.28 (m, 2H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.67 (d, *J* = 12.4, 1H), 4.44 (d, *J* = 12.4 Hz, 1H), 4.32 (ddd, *J* = 9.6, 6.8, 0.8 Hz, 1H), 4.22 (q, *J* = 6.4 Hz, 1H), 3.94 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.69 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.39 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.1, 135.0, 131.7, 128.2, 127.9, 127.5, 127.2, 120.4, 109.8, 77.9, 74.9,69.9, 65.7, 26.5, 25.3. HRMS Calcd. for $C_{17}H_{23}O_3$ (M+1): 275.1647, Found: 275.1646.



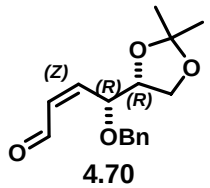
4.74

(*Z,4R*)-4-((*1S*)-1-Benzyloxy-penta-2,4-dienyl)-2,2-dimethyl-[1,3]dioxolane (4.74). R_f = 0.3, Hexane/EA = 10/1; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.35 – 7.24 (m, 5H), 6.54 (dt, *J* = 16.8, 11.0 Hz, 1H), 6.31 (t, *J* = 11.0 Hz, 1H), 5.43 (t, *J* = 10.2, 1H), 5.31 (d, *J* = 16.4 Hz, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 12.0, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.23 (dd, *J* = 9.2, 6.4 Hz, 1H), 4.12 (dd, *J* = 11.6, 6.4 Hz, 1H), 4.06 (dd, *J* = 8.2, 6.2 Hz, 1H), 3.89 (dd, *J* = 8.4, 5.6 Hz, 1H), 1.39 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (75

MHz, $CDCl_3$): 138.0, 134.8, 131.5, 128.4, 128.3, 127.9, 127.6, 120.1, 109.4, 77.5, 74.7, 70.1, 66.7, 26.4, 25.1. HRMS Calcd. for $C_{17}H_{23}O_3$ (M+1): 275.1647, Found: 275.1646.

Representative Procedure for Site-Selective Oxidative Cleavage

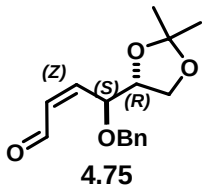
To a mixture of THF and water (11.7mL, 0.05M,THF:wate = 2.5:1), OsO_4 (3.0 mg, 5 mol%) and diene **4.69** (64.0 mg, 100 mol%) was added and then stirred for 5 minutes. While the temperature of the stirred mixture was maintained at 24 – 26 °C, $NaIO_4$ (110.0 mg, 220 mol%) was added in portions over a period of 40 minutes. The solution was stirred for an additional 2 hours. The mixture was extracted thoroughly with ether and the combined organic layers were dried with Na_2SO_4. The solvent was removed *in vacuo*, and then the title compound was purified by flash silical chromatography (R_f = 0.3, Hexane/EA = 4/1) to afford 59.8 mg of **4.70** as a colorless oil (85 % yield).



4.70

(*Z,4R*)-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enal (4.70). R_f = 0.3, Hexane/EA = 4/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 9.89 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.24 (m, 5H), 6.47 (dd, *J* = 16.0, 8.8 Hz, 1H), 6.17 (dd, *J* = 11.6, 7.6 Hz, 1H), 4.78 (dd, *J* = 9.2, 5.2 1H), 4.68 (d, *J* = 12.6 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.31 (q, *J* = 6.0, 1H), 3.99 (dd, *J* = 8.6, 7.0 Hz, 1H), 3.87 (dd, *J* = 9.0, 5.8 Hz, 1H), 1.33 (3, 3H), 1.31 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 191.0, 146.6, 137.1, 133.6, 128.5, 128.1,

127.8, 110.0, 73.9, 71.5, 65.0, 26.1, 25.0. HRMS Calcd. for $C_{16}H_{20}O_4$ (M): 276.1365, Found: 276.1362.



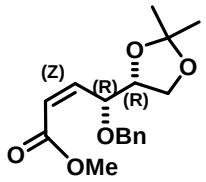
4.75

(*Z*,*4S*)-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enal (4.75). R_f = 0.3, Hexane/EA = 4/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 9.93 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.26 (m, 5H), 6.48 (dd, *J* = 11.6, 8.8 Hz, 1H), 6.19 (ddd, *J* = 11.5, 7.5, 0.9 Hz, 1H), 4.64 (d, *J* = 11.6, 1H), 4.61 (d, *J* = 8.8 Hz, 1H), 4.61 (q, *J* = 8.8, 1H), 4.43 (d, *J* = 11.6, 7.0 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.94 – 3.89 (m, 1H), 1.36 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 190.7, 148.0, 136.9, 133.5, 128.6, 128.2, 127.9, 109.9, 76.5, 75.0, 71.4, 67.1, 26.4, 24.8. HRMS Calcd. for $C_{16}H_{20}O_4$ (M+1): 277.1440, Found: 277.1437.

Representative Procedure for the Oxidation of Enal to α,β-Unsaturated Ester

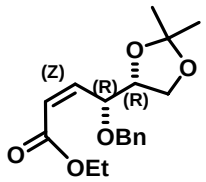
To a solution of aldehyde **4.70** (37.9 mg, 0.137 mmol, 100 mol%) in MeOH (2.74 mL, 0.05M) was added manganese dioxide (280 mg, 2.74 mmol, 20 eq.) and sodium cyanide (28.3 mg, 0.55 mmol, 400 mol%). The resulting suspension was stirred at room temperature for 3 hrs, filtered (Celite) and the filtrate was evaporated under reduced pressure. The residue was redissolved in water and extracted with ether. The combined organic extracts were dried with Na_2SO_4 and evaporated. The residue was purified by

flash silical chromatography (Rf = 0.3, Hexane/EA=6/1) to afford 39.1 mg of **4.71** as a colorless oil (93% yield).



4.71

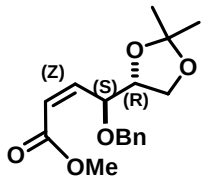
(*Z,4R*)-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester (4.71). Rf = 0.3, Hexane/EA=6/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 – 7.23 (m, 5H), 6.17 (dd, *J* = 12.0, 9.0 Hz, 1H), 5.99 (dd, *J* = 11.7, 0.9 Hz, 1H), 5.14 (ddd, *J* = 9.2, 5.2, 1.1 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 12.1 Hz, 1H), 4.26 – 4.20 (m, 1H), 3.97 – 3.87 (m, 2H), 3.68 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.1, 146.2, 138.1, 128.2, 127.7, 127.6, 123.1, 109.8, 77.6, 74.4, 71.5, 65.3, 51.5, 26.2, 25.5. HRMS Calcd. for $C_{16}H_{20}O_4$ (M): 307.1545, Found: 307.1543.



4.72

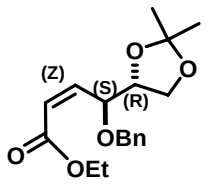
(*Z,4R*)-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid ethyl ester (4.72). Rf = 0.3, Hexane/EA=6/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 – 7.22 (m, 5H), 6.15 (dd, *J* = 11.6, 9.2 Hz, 1H), 5.97 (d, *J* = 12.2 Hz, 1H), 5.13 (dd, *J* = 9.0, 2.4 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.25 – 4.19 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.96 – 3.86 (m, 2H), 1.40 (s, 3H), 1.34 (s, 3H), 1.23 (t, *J* = 7.1Hz,

3H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.5, 145.7, 138.1, 128.2, 127.8, 127.6, 123.6, 109.8, 77.6, 74.4, 71.4, 65.3, 60.4, 26.2, 25.5, 14.1. HRMS Calcd. for $C_{16}H_{20}O_4$ (M): 321.1702, Found: 321.1706.



4.76

(*Z,4S*)-4-Benzyloxy-4-((*4R*)-42,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid methyl ester (4.76). Rf = 0.3, Hexane/EA=6/1; colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$): 7.33 – 7.25 (m, 5H), 6.16 (dd, *J* = 12.2, 9.0 Hz, 1H), 6.06 (dd, *J* = 11.6, 0.8 Hz, 1H), 5.14 (ddd, *J* = 9.2, 5.6, 0.8, 1H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.19 (q, *J* = 6.0 Hz, 1H), 4.03 (dd, *J* = 8.4, 5.6 Hz, 1H), 4.03 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.84 (dd, *J* = 8.6, 6.2 Hz, 1H), 3.68 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): 166.0, 145.5, 137.9, 128.3, 127.9, 127.7, 123.8, 109.5, 74.4, 71.5, 66.3, 51.4, 51.4, 26.2, 25.2. **HRMS** Calcd. for $C_{16}H_{20}O_4$ (M): 307.1545, Found: 307.1545.



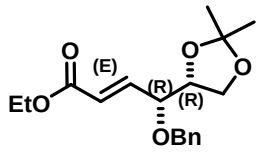
4.77

(*Z,4S*)-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid ethyl ester (4.77). Rf = 0.3, Hexane/EA=6/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 – 7.25 (m, 5H), 6.15 (dd, *J* = 11.7, 8.7 Hz, 1H), 6.05 (d, *J* = 11.7 Hz, 1H), 5.15 (dd, *J* = 9.0, 5.4 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.22 – 4.10 (m, 2H),

4.02 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.85 (dd, *J* = 11.6, 5.9, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.24 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.7, 145.2, 137.9, 128.3, 127.9, 127.7, 125.3, 109.5, 77.4, 74.3, 71.4, 66.2, 60.4, 26.1, 25.2, 14.1. HRMS Calcd. for $C_{16}H_{20}O_4$ (M): 321.1702, Found: 321.1698.

Representative Procedure for *cis-trans* Isomerization of α,β-Unsaturated Ester

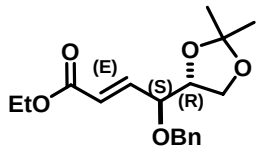
To a solution of *Z*-ester **4.72** (31.5 mg, 0.098 mmol, 100 mol%) in *t*-BuOH (4.9 mL, 0.05M) was added trimethylphosphine in toluene (39.2μL, 0.039, 40 mol%). The resulting solution was stirred at 35 ^{o}C for 12 hrs. *t*-BuOH was evaporated. The residue was purified by flash silical chromatography (Rf = 0.3, Hexane/EA=6/1) to afford 28.9 mg of **4.73** as a colorless oil (92% yield).



4.73

(*Z,4R*)-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid ethyl ester (4.73). Rf = 0.3, Hexane/EA=6/1; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.35 – 7.25 (m, 5H), 6.82 (dd, *J* = 15.8, 6.2 Hz, 1H), 6.09 (d, *J* = 15.6 Hz, 1H), 4.67 (d, *J* = 12.0, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.25 – 4.17 (m, 3H), 4.77 (t *J* = 6.4 Hz, 1H), 3.96 (dd, *J* = 8.6, 6.6 Hz, 1H), 3.77 (dd, *J* = 8.6, 6.2 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H), 1.28 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.7, 143.3, 128.4, 127.8, 127.7, 124.4, 109.8,

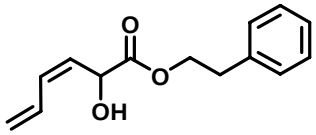
78.2, 71.5, 65.3, 60.6, 26.2, 25.1, 14.2. HRMS Calcd. for $C_{16}H_{20}O_4$ (M): 321.1702, Found: 321.1701.



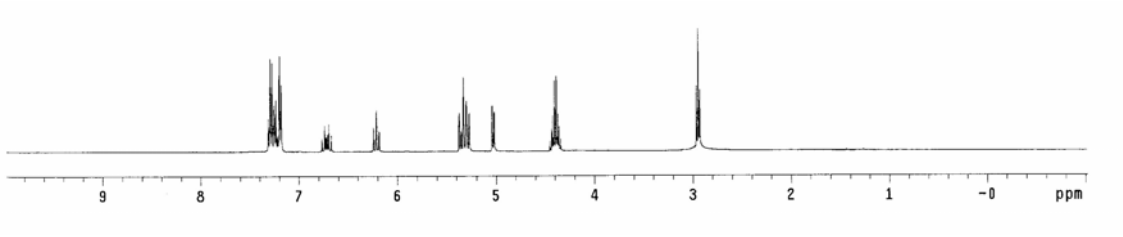
4.78

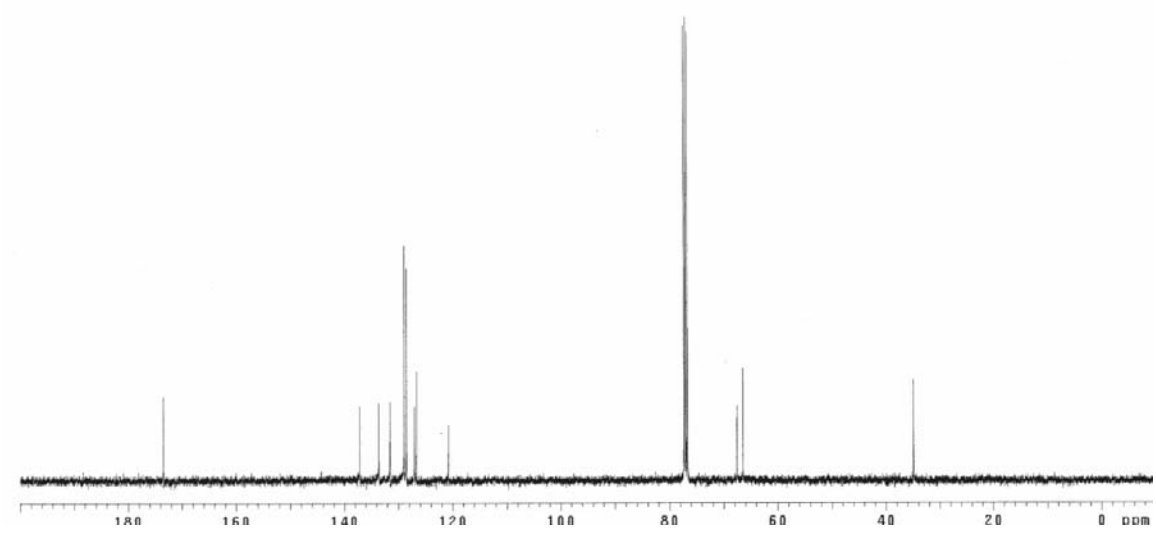
(*E,4S)*-4-Benzyloxy-4-((*4R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-2-enoic acid ethyl ester (4.78). Rf = 0.3, Hexane/EA=6/1; a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 – 7.25 (m, 5H), 6.89 (dd, *J* = 15.9, 6.0 Hz, 1H), 6.08 (dd, *J* = 15.9, 1.5 Hz, 1H), 4.63 (d, *J* = 11.4, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.20 (q, J = 7.1, 2H), 4.12 – 4.00 (m, 2H), 3.94 (td, *J* = 6.3, 1.1 Hz, 1H), 3.87 (dd, *J* = 8.1, 5.1 Hz, 1H), 1.39 (s, 3H), 1.32 (s, 3H), 1.29 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.7, 143.3, 128.4, 127.8, 127.7, 124.4, 109.8, 78.2, 71.5, 65.3, 60.6, 26.2, 25.1, 14.2. HRMS Calcd. for $C_{16}H_{20}O_4$ (M): 321.1702, Found: 321.1701.

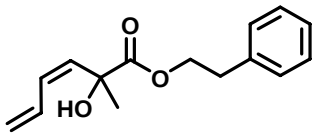
4.7 SPECTRA



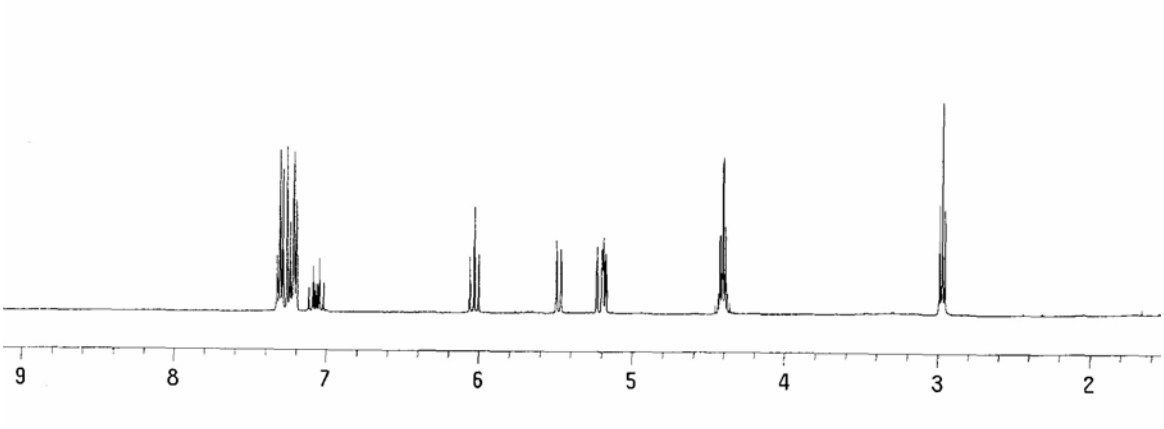
4.2

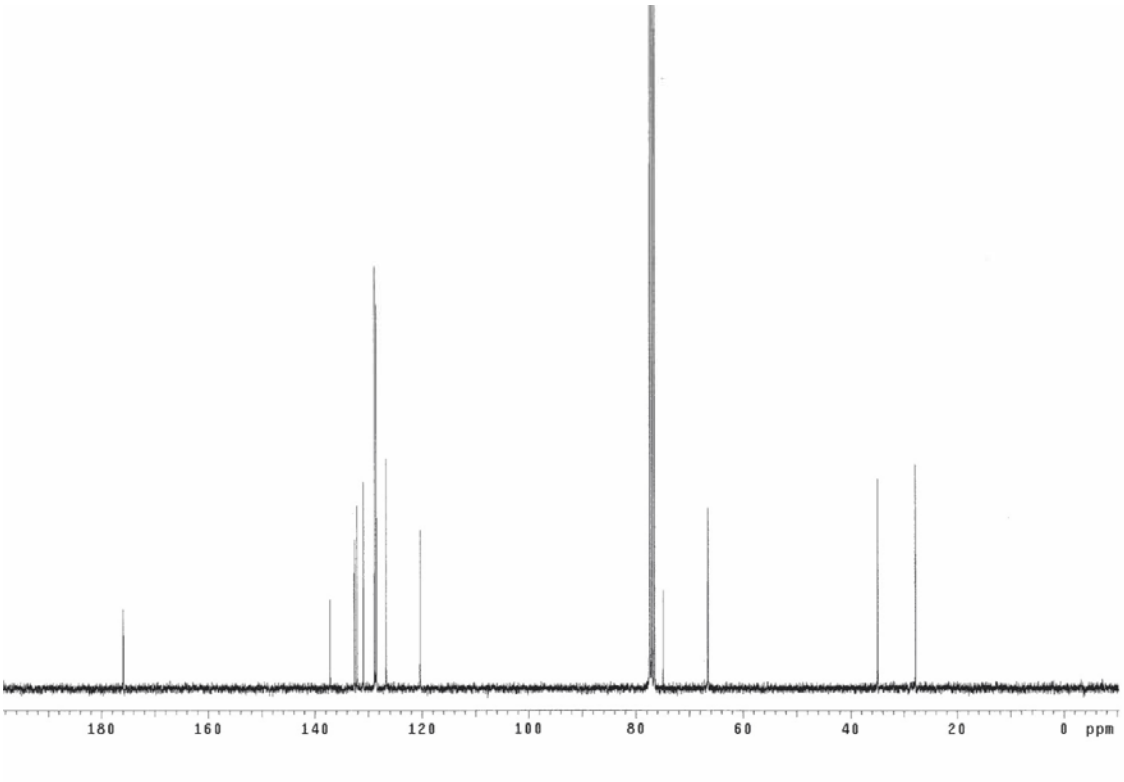


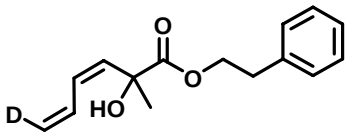




4.3







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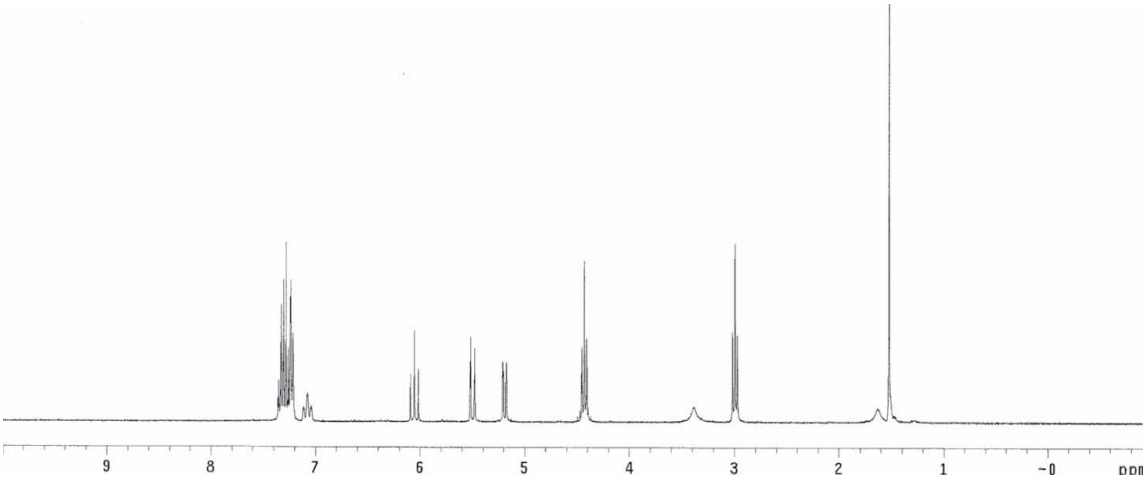

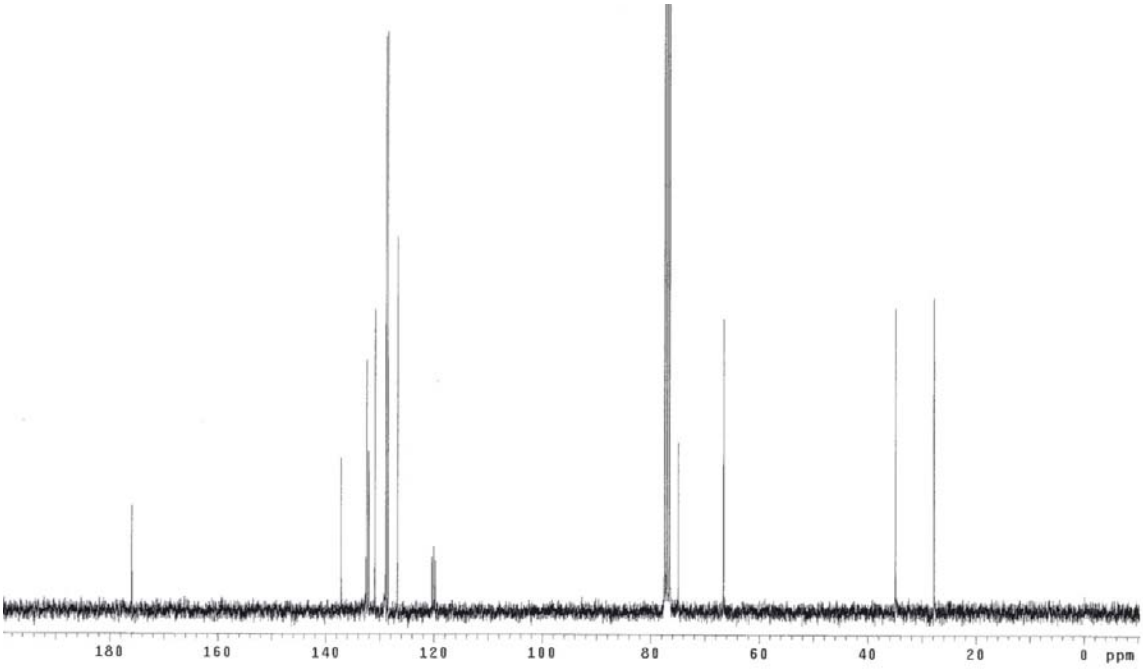

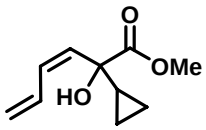

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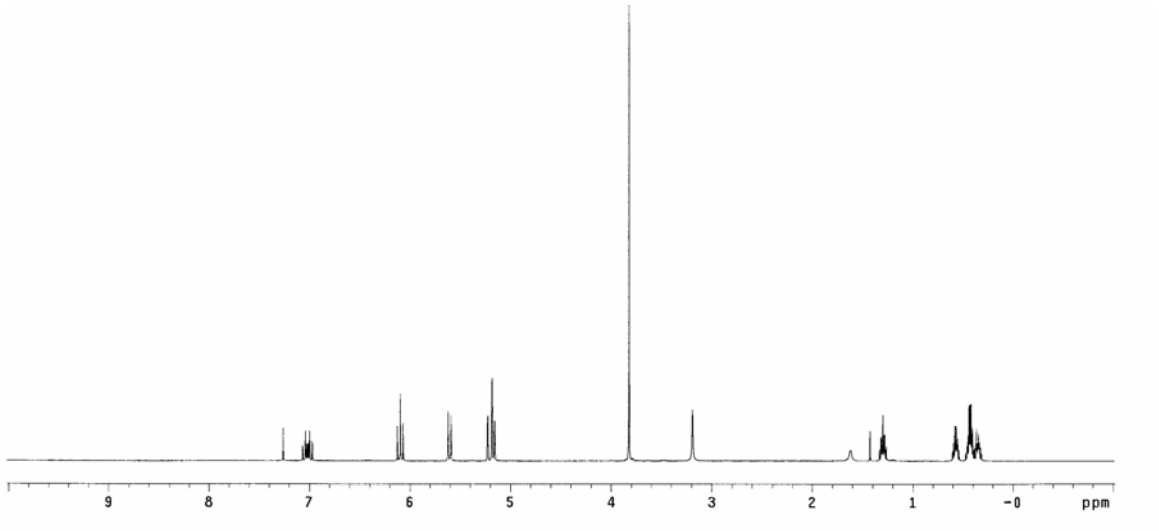

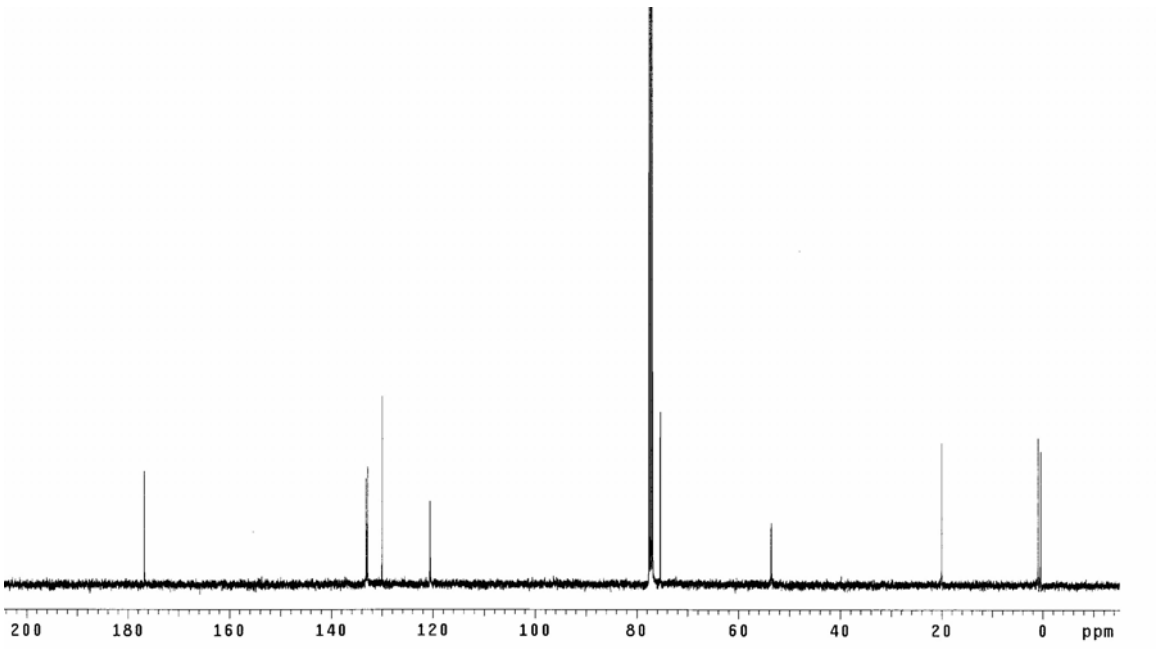

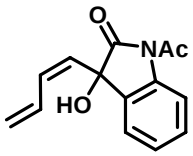

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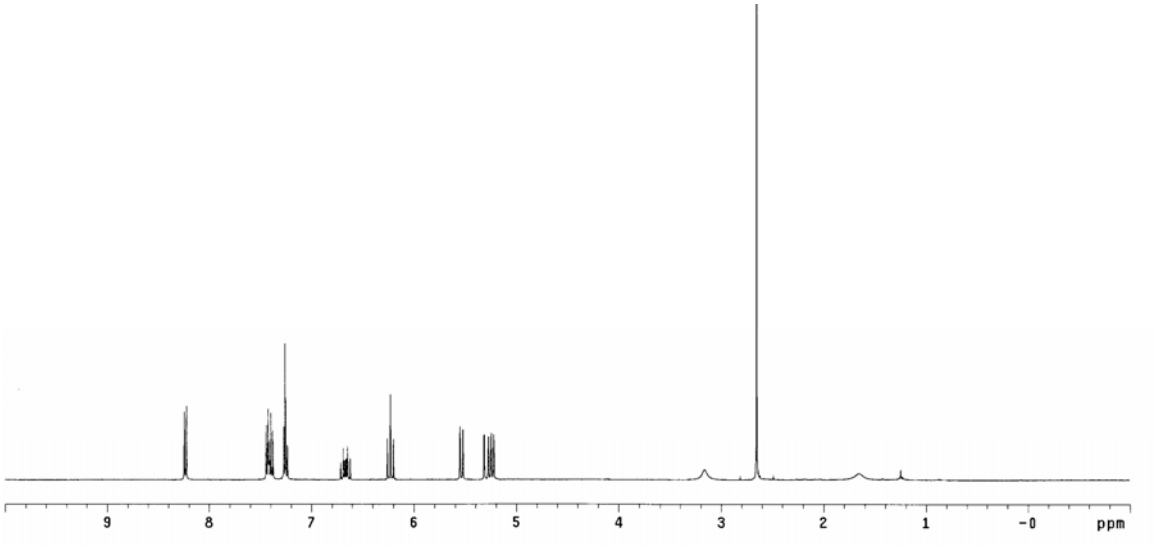

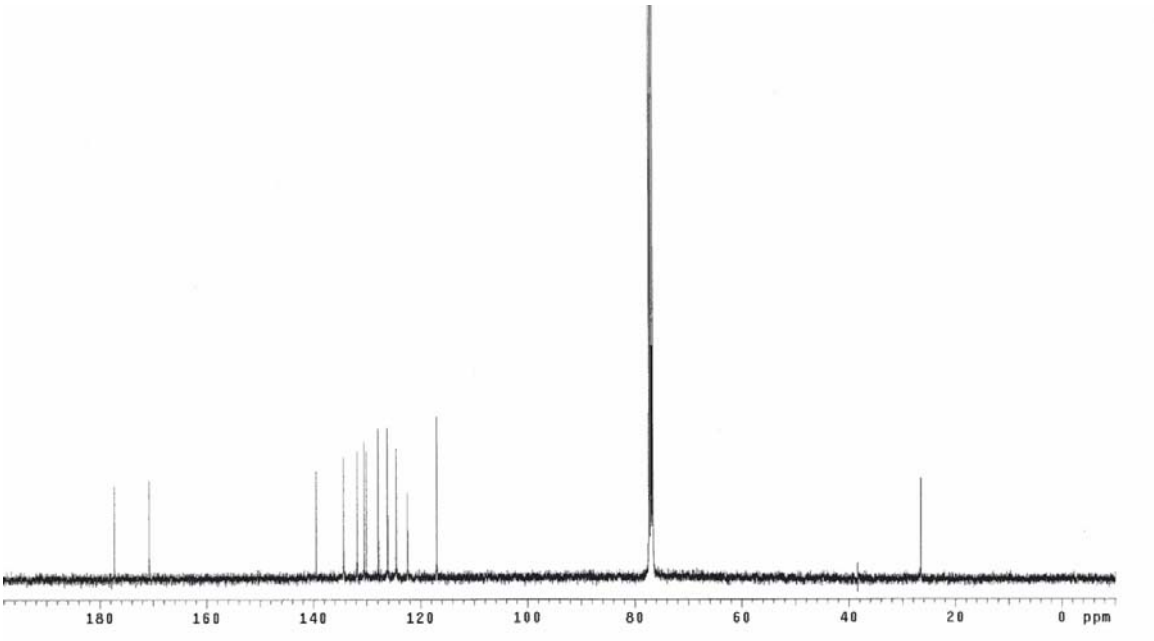

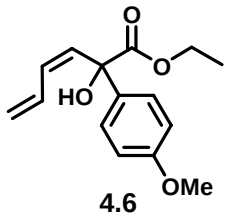

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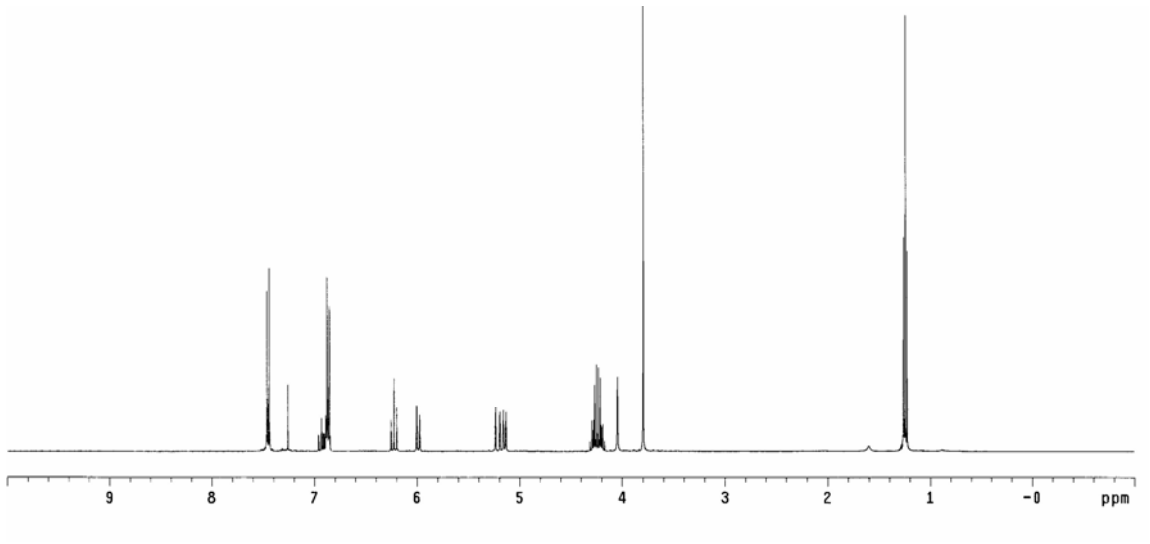

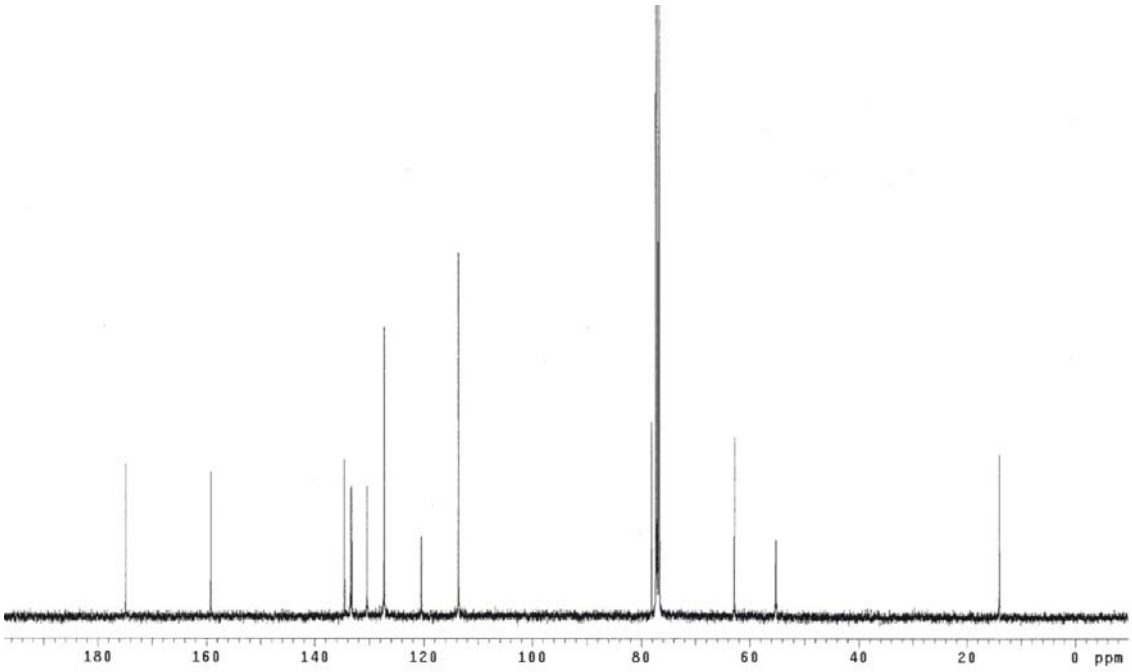

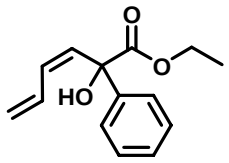

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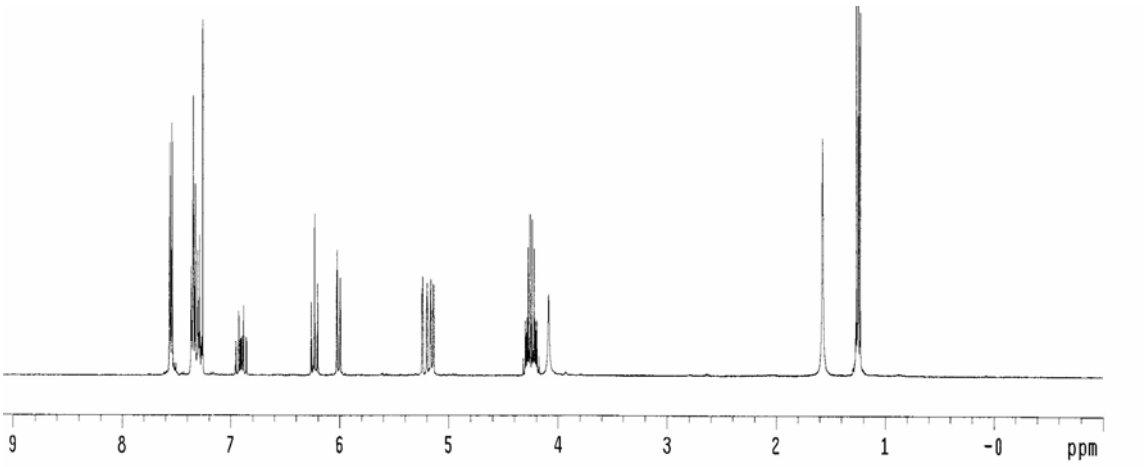

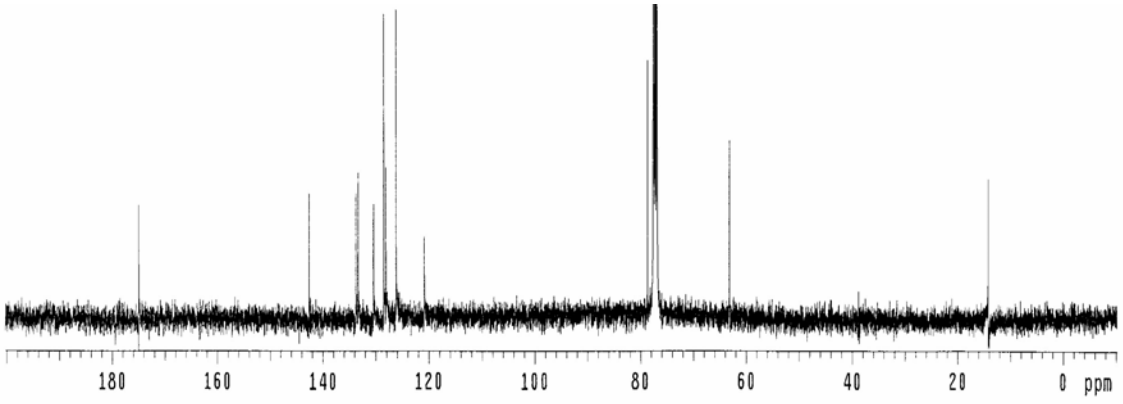

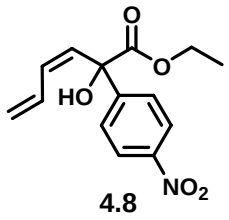

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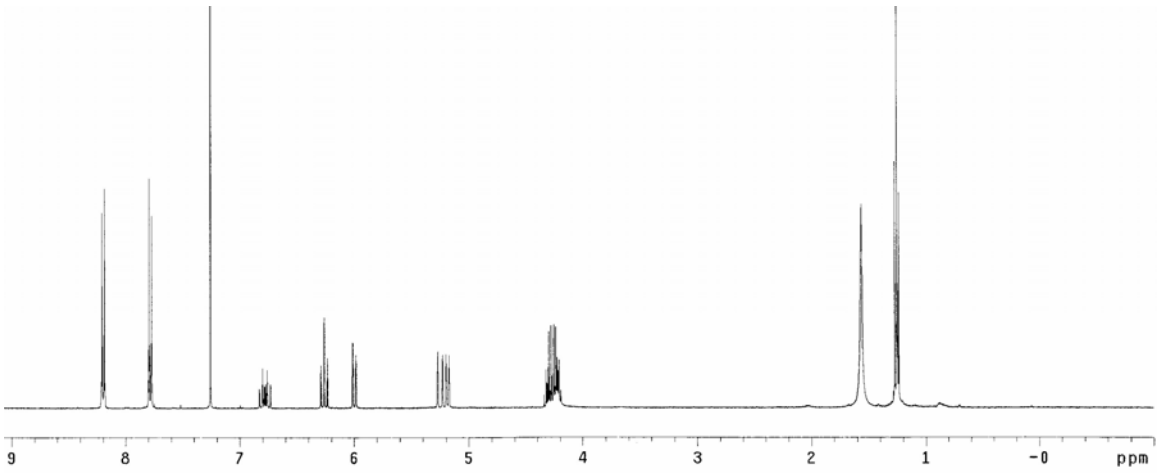

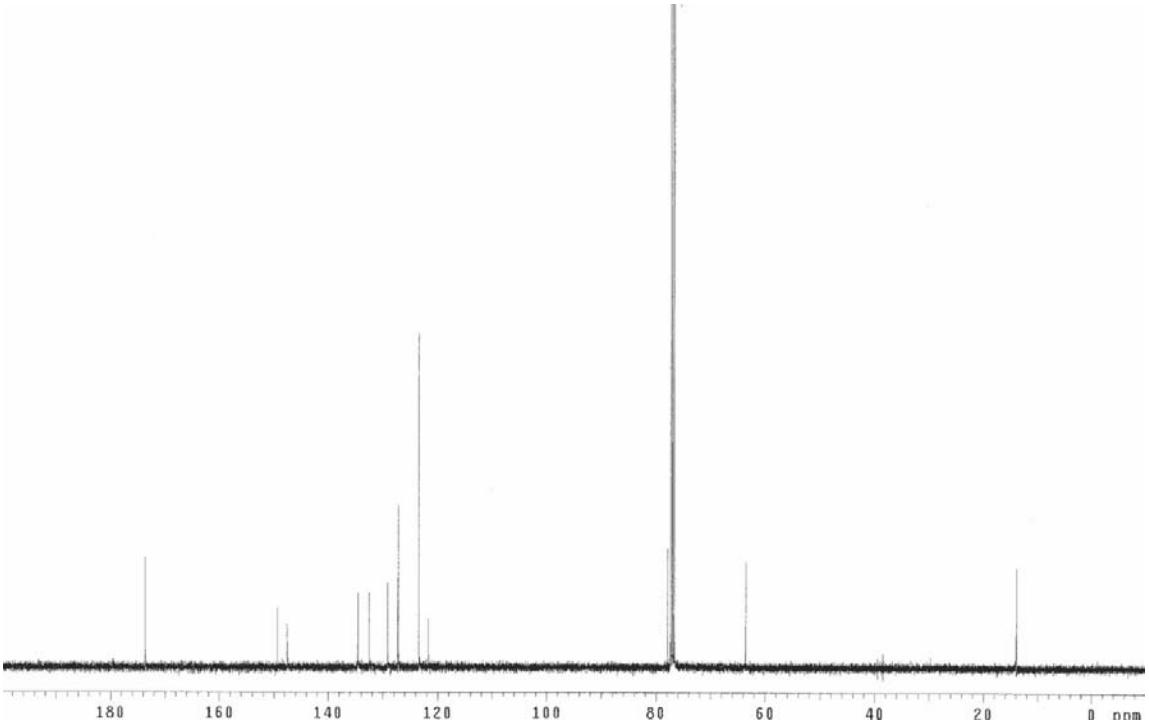

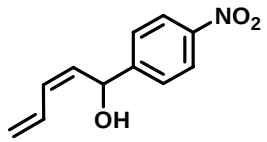

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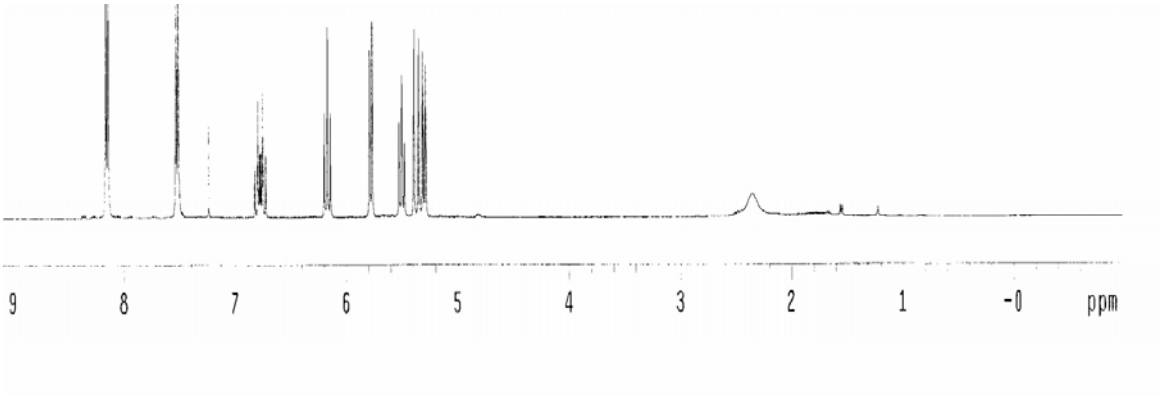

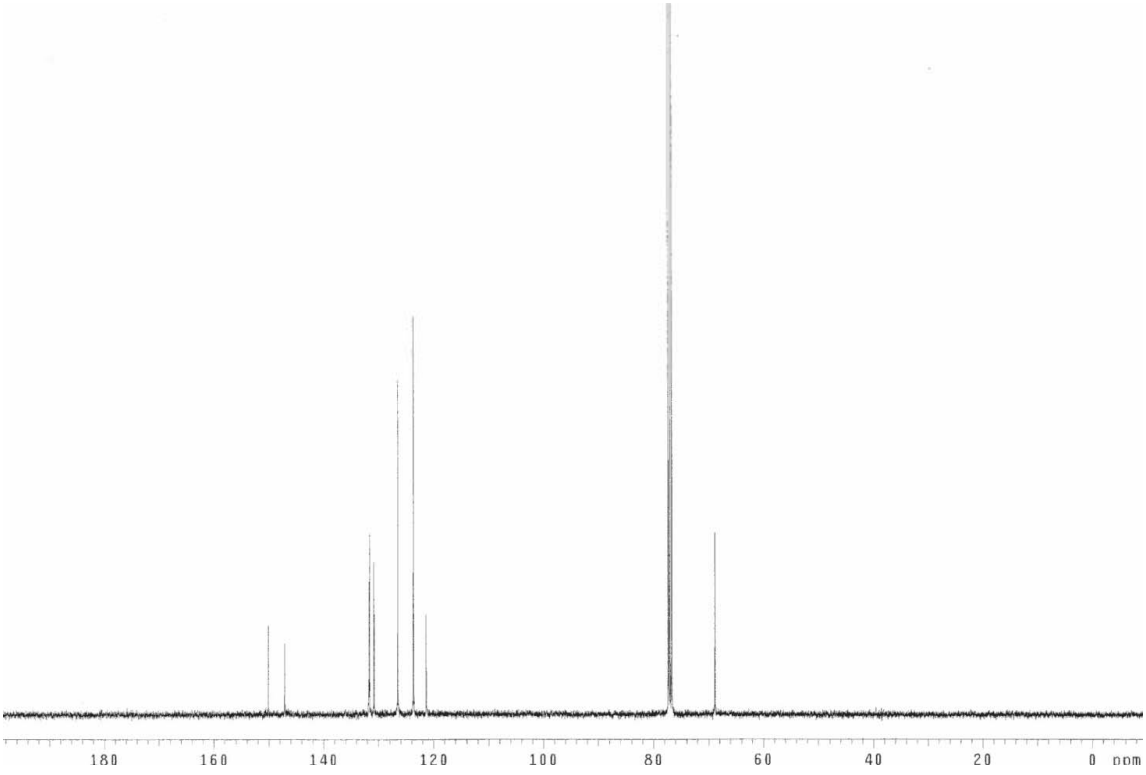

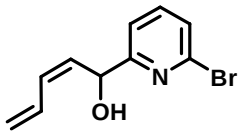

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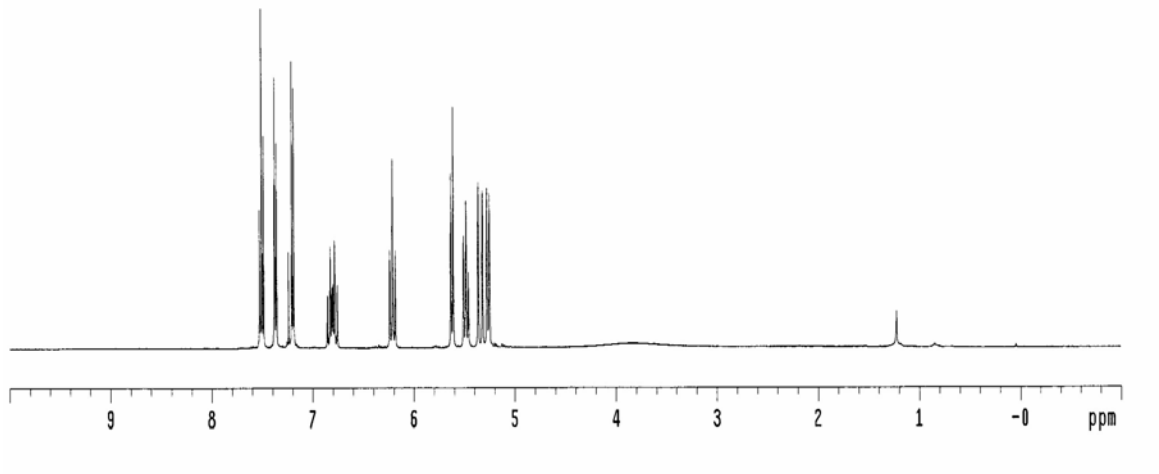

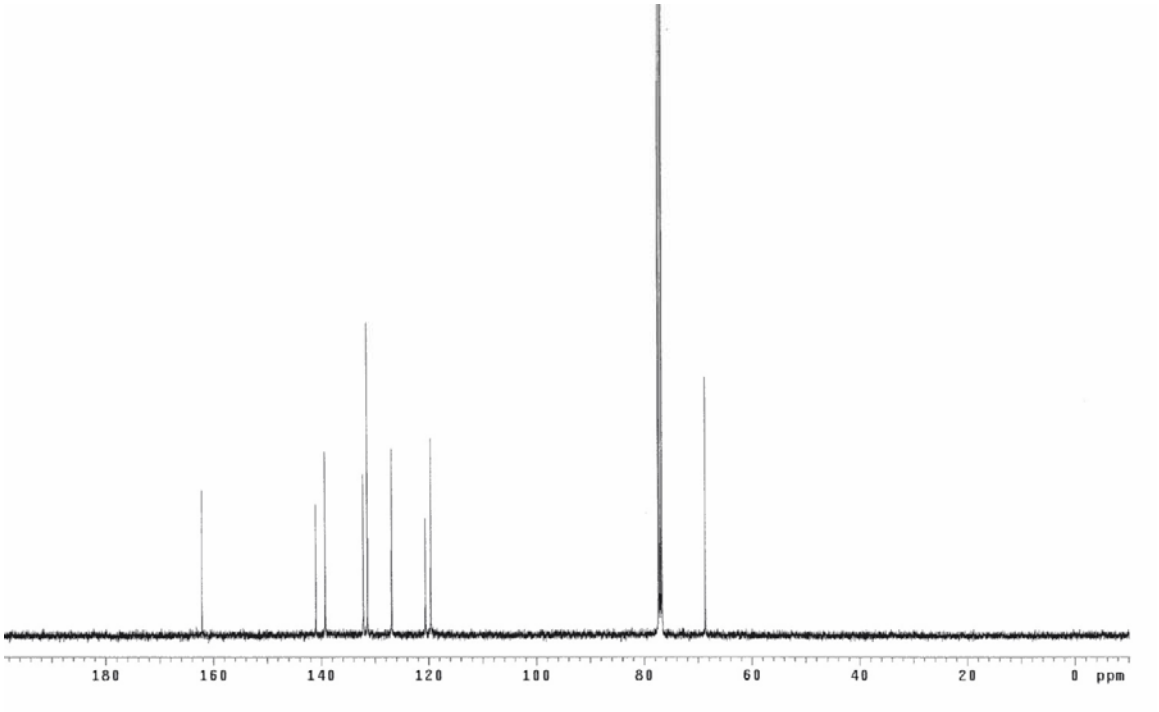

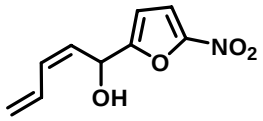

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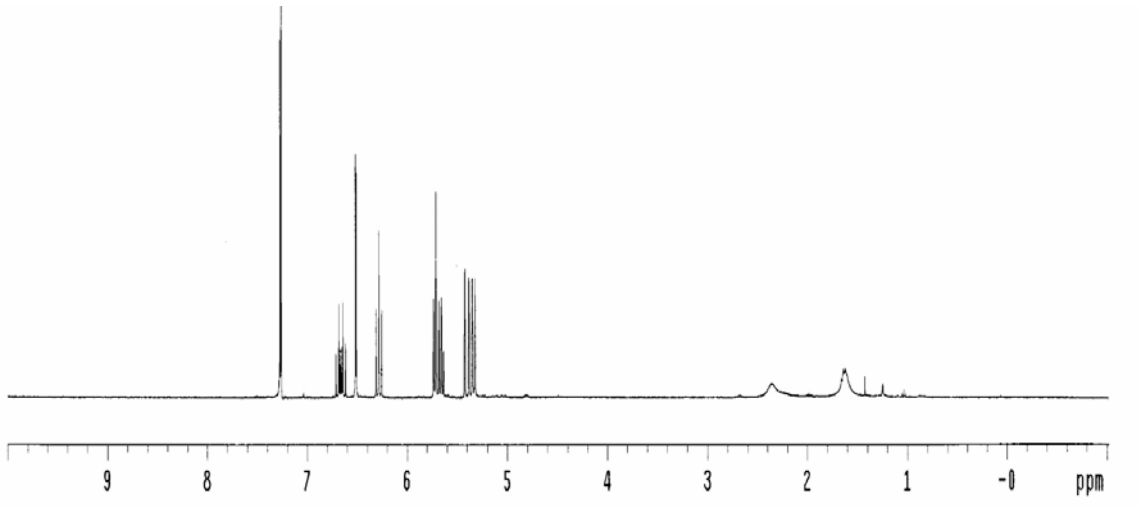

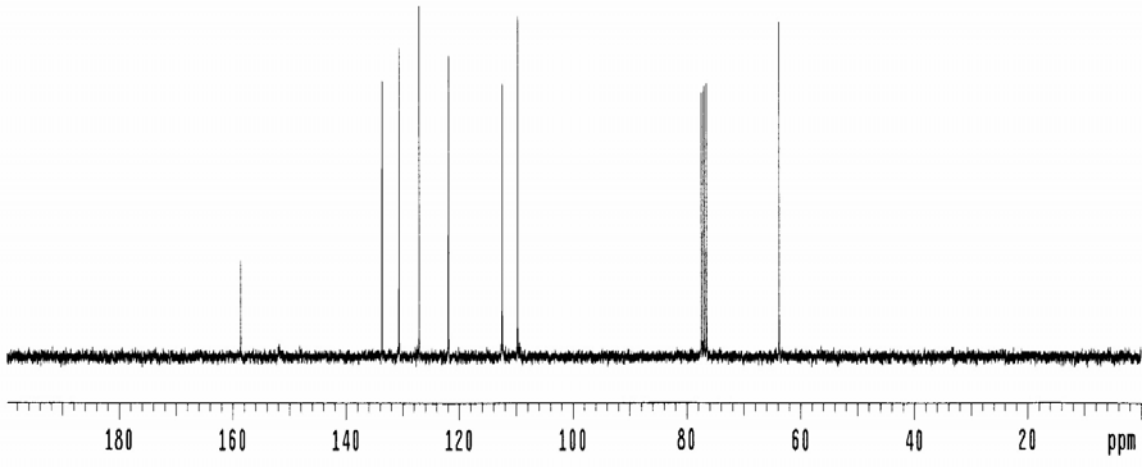

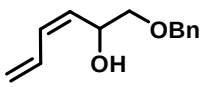

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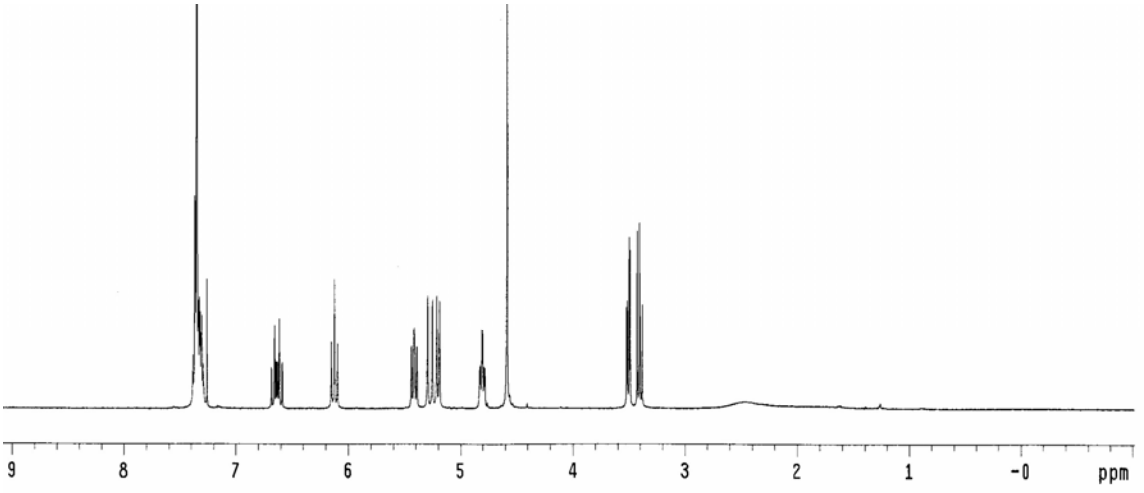

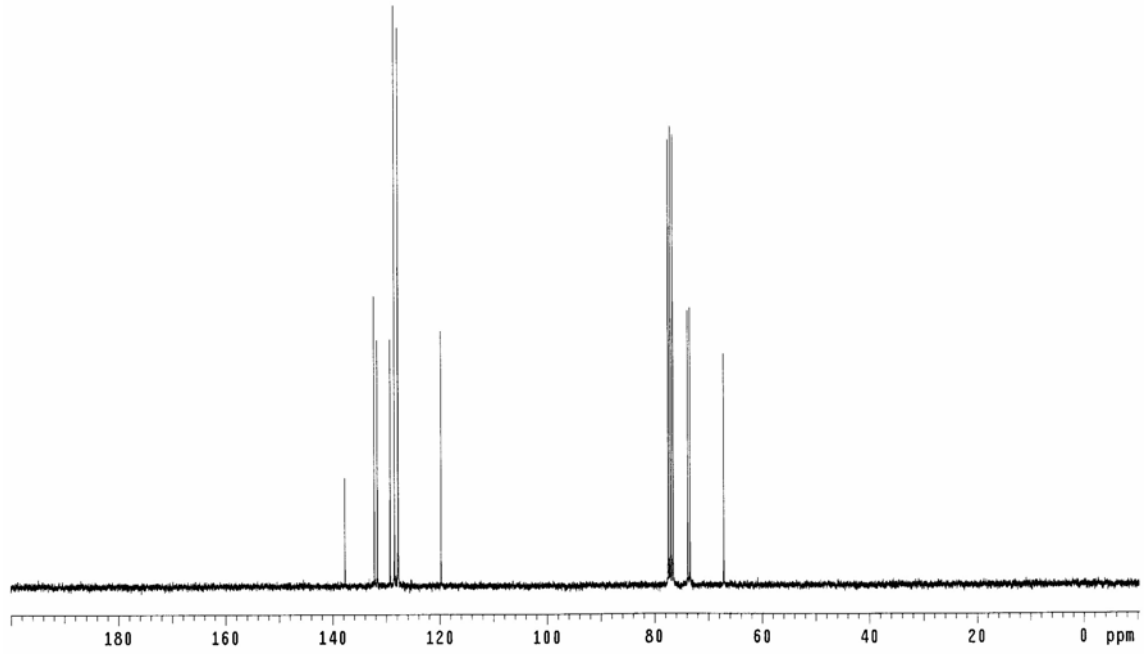

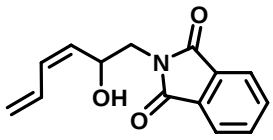

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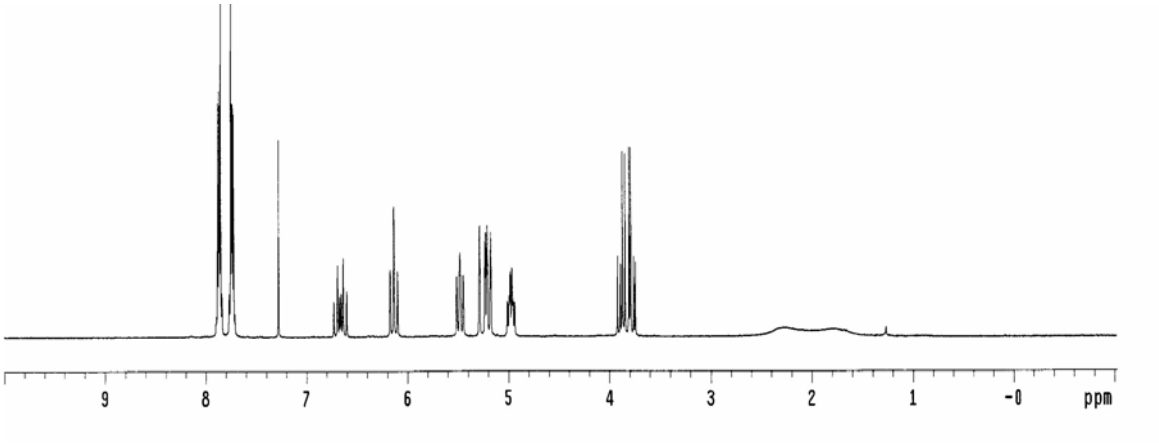

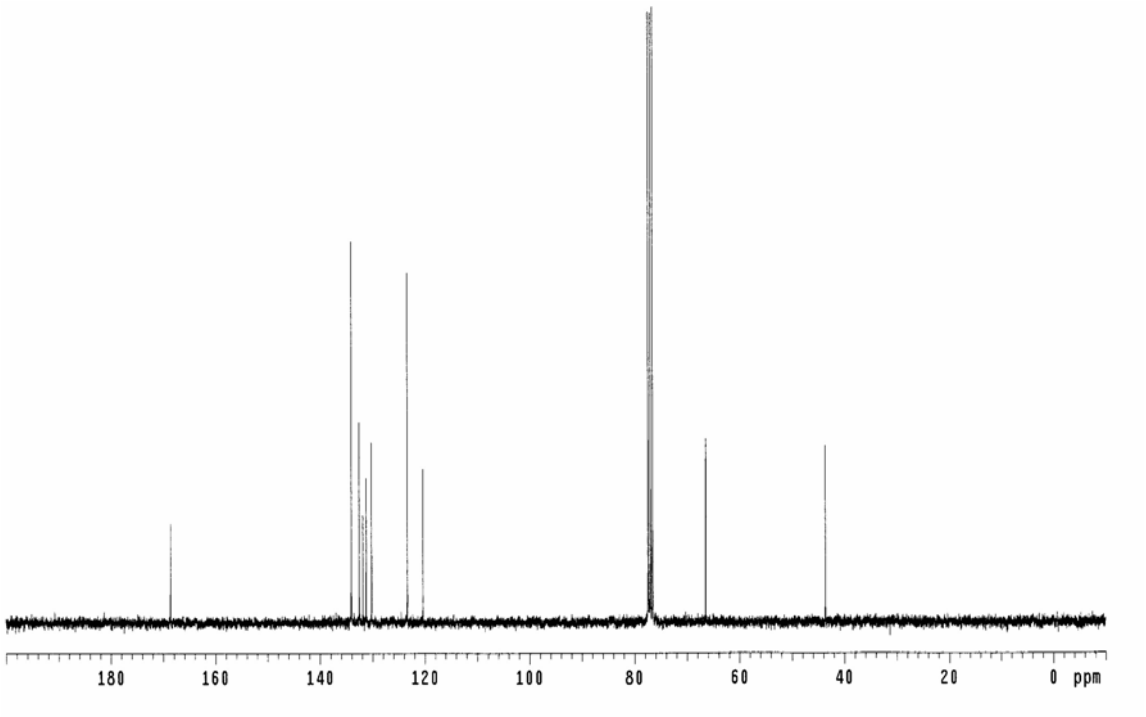

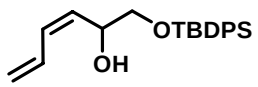

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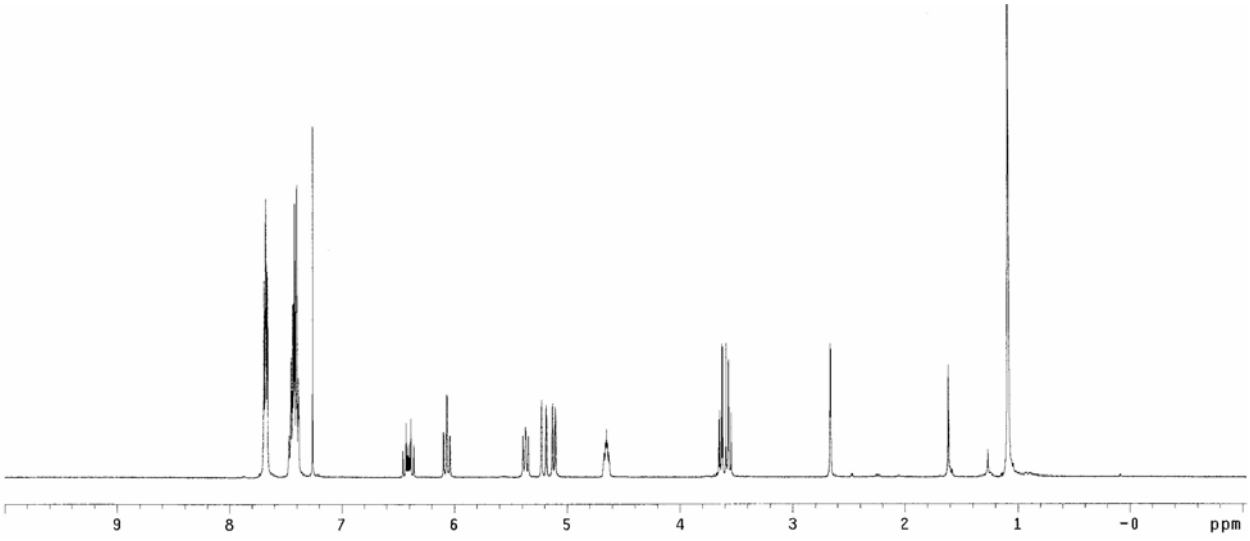

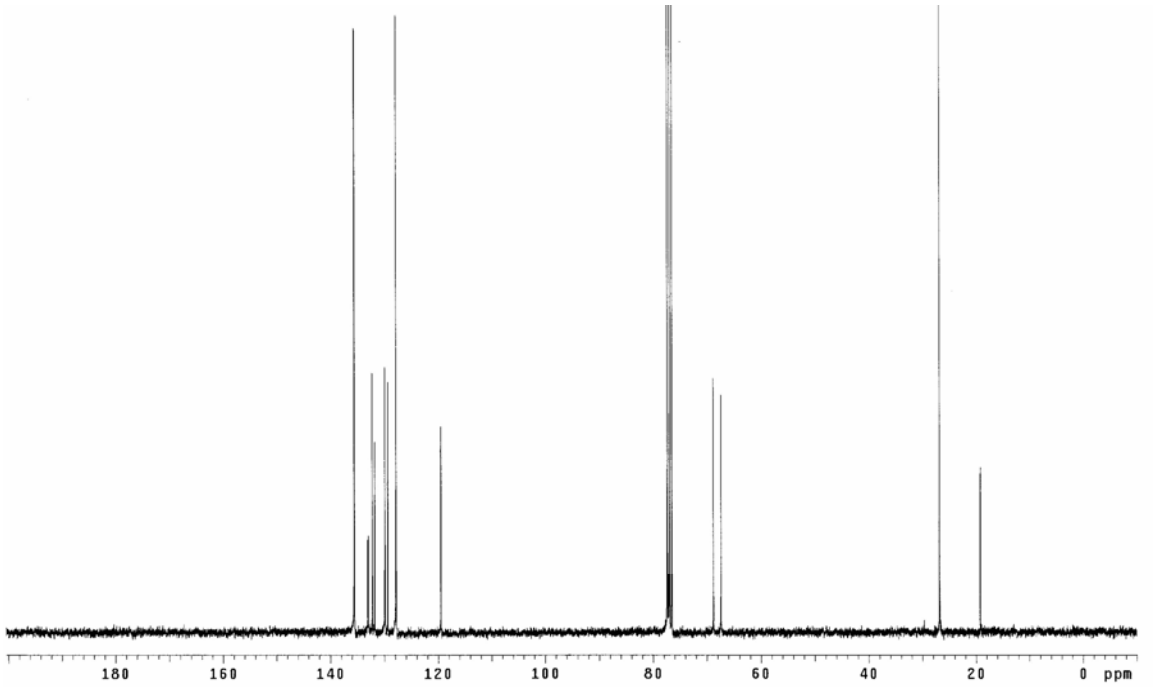

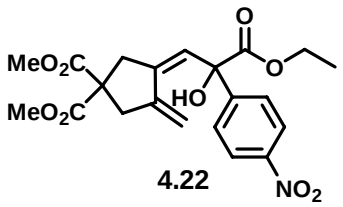
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O
HO
MeO2C
NO2

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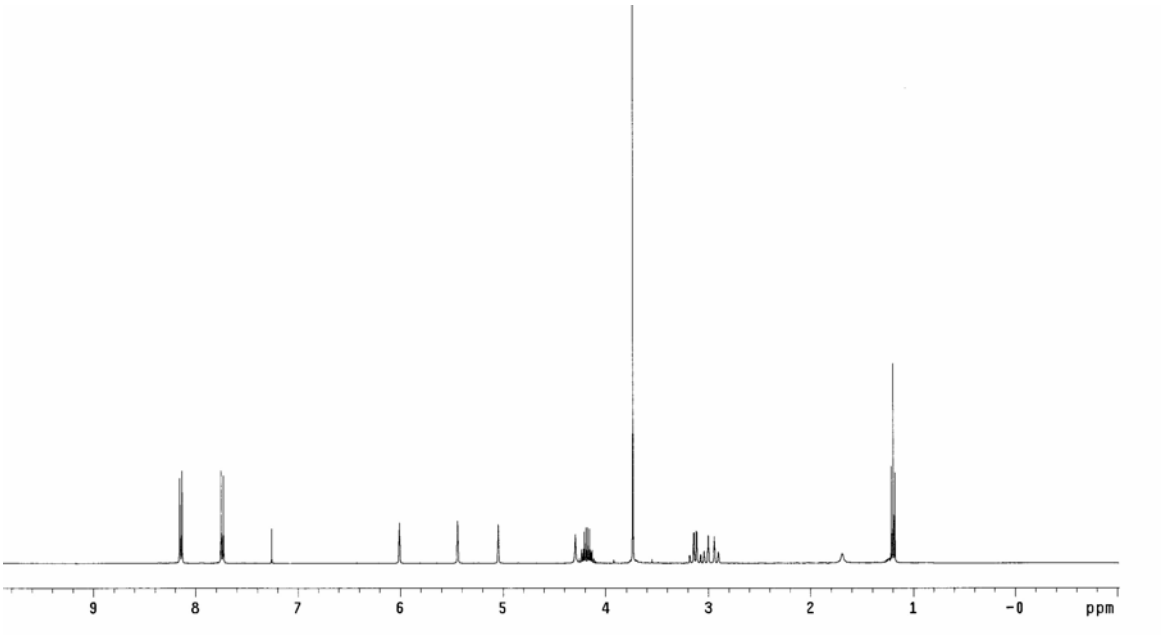
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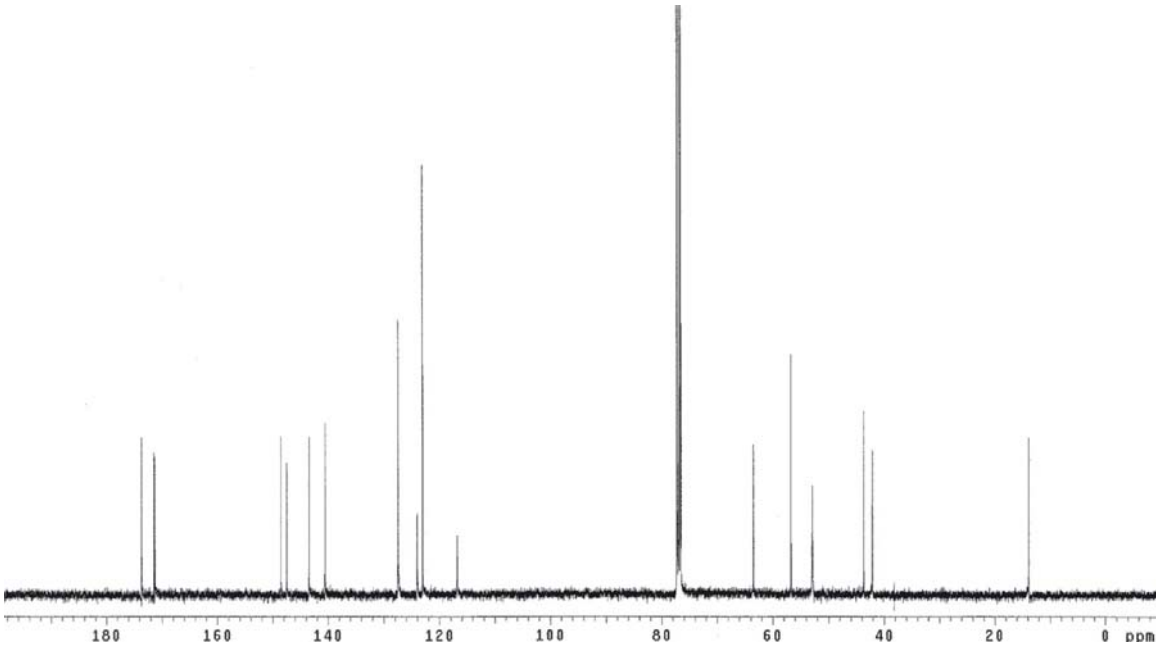
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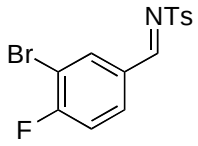
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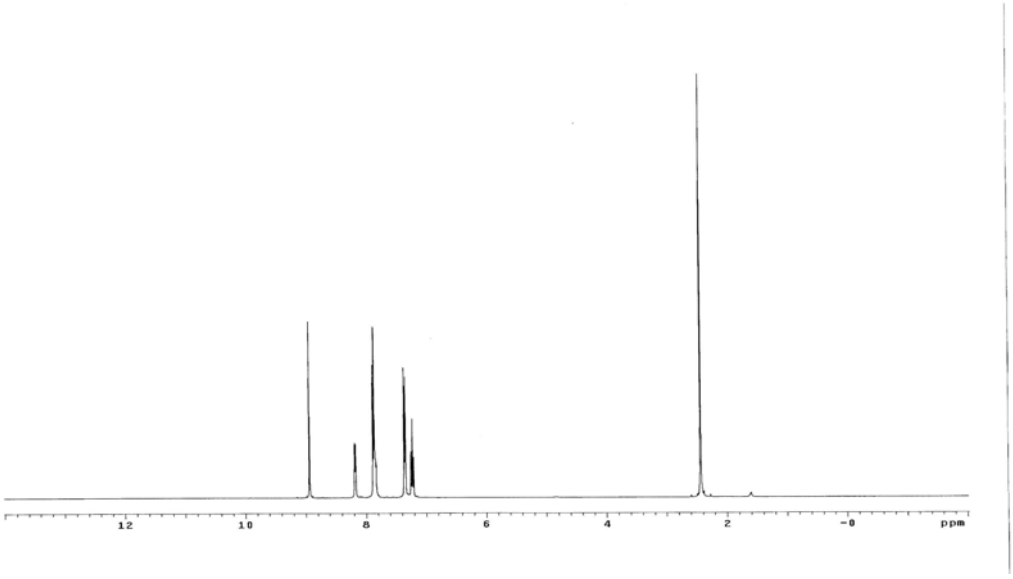
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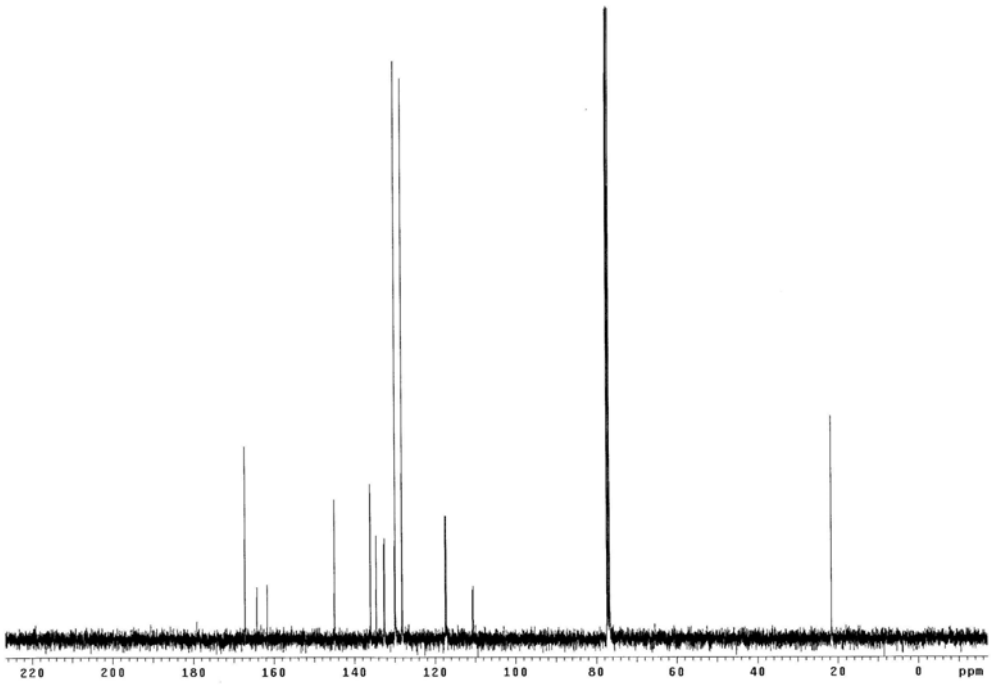
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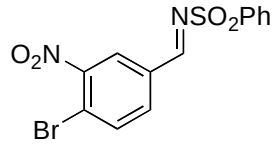
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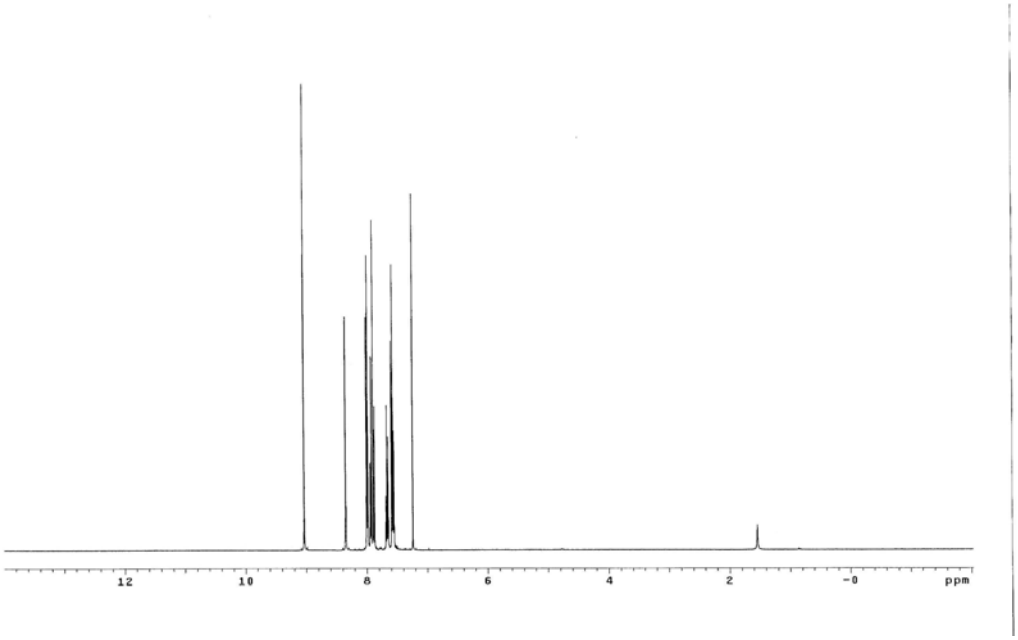
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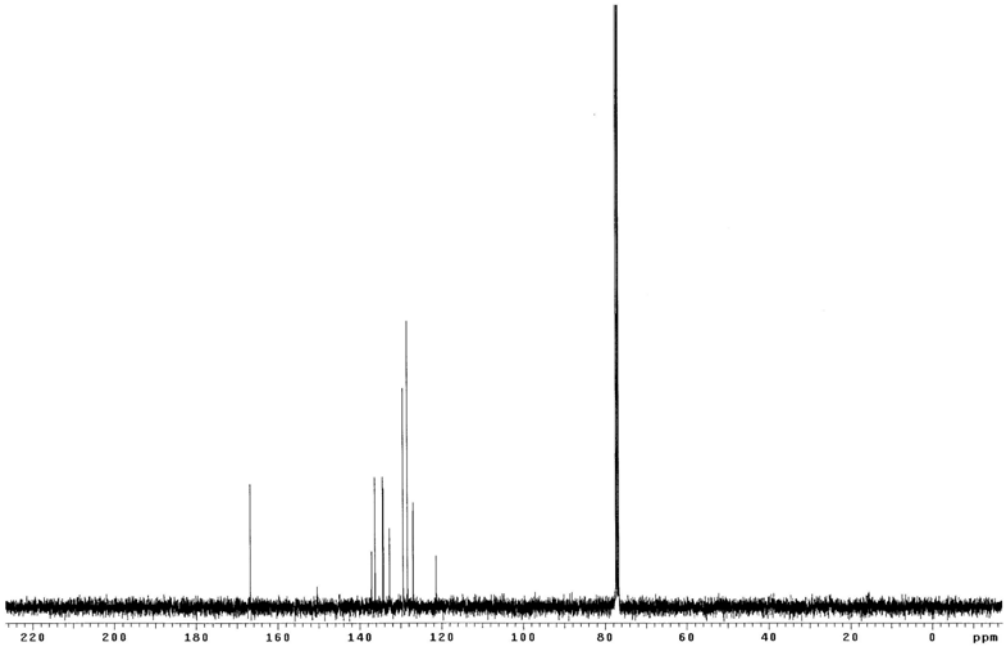
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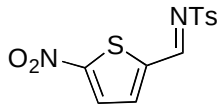
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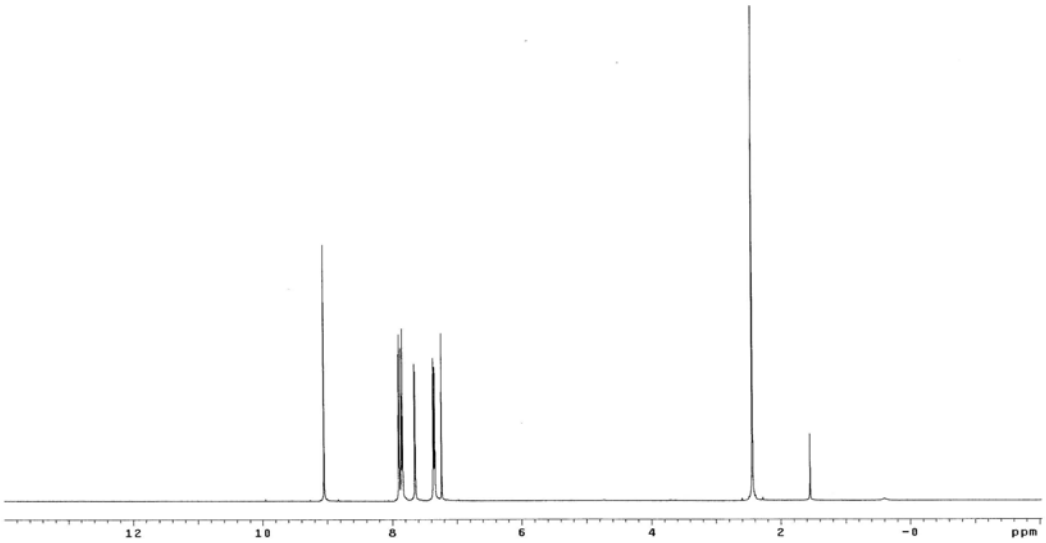
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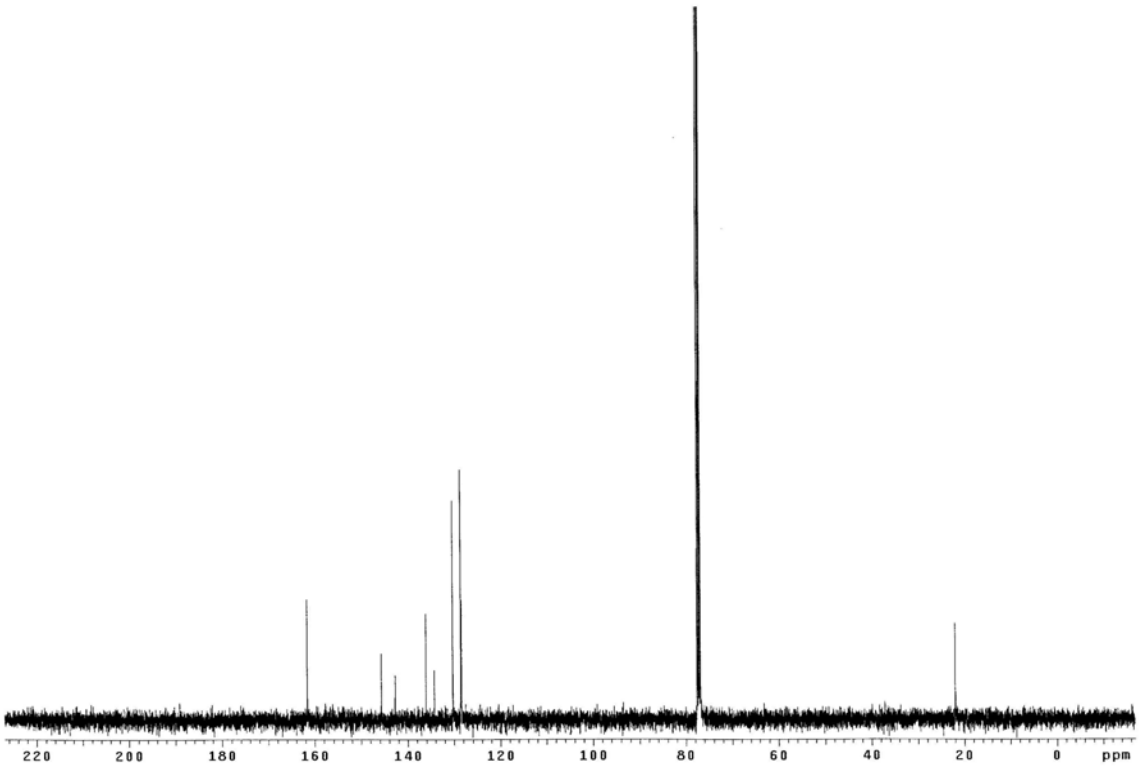
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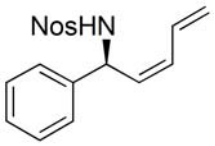
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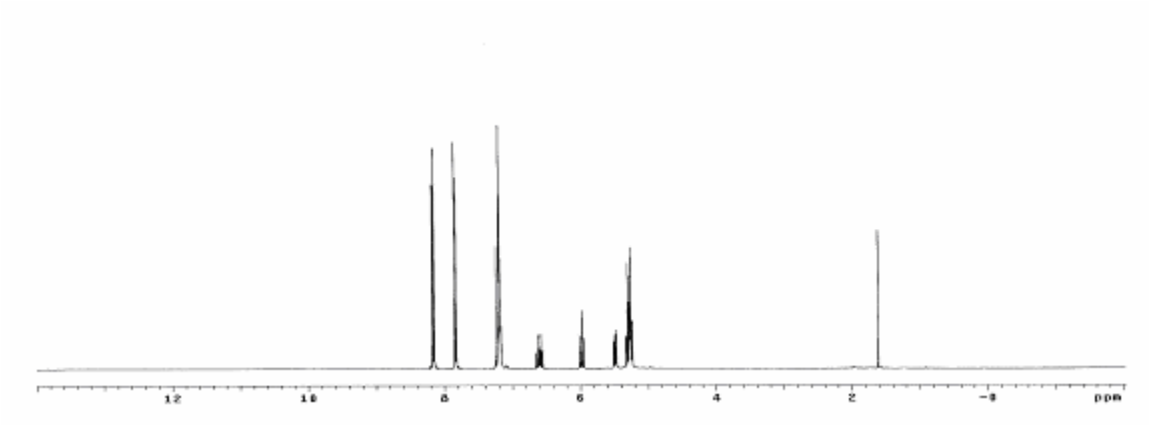
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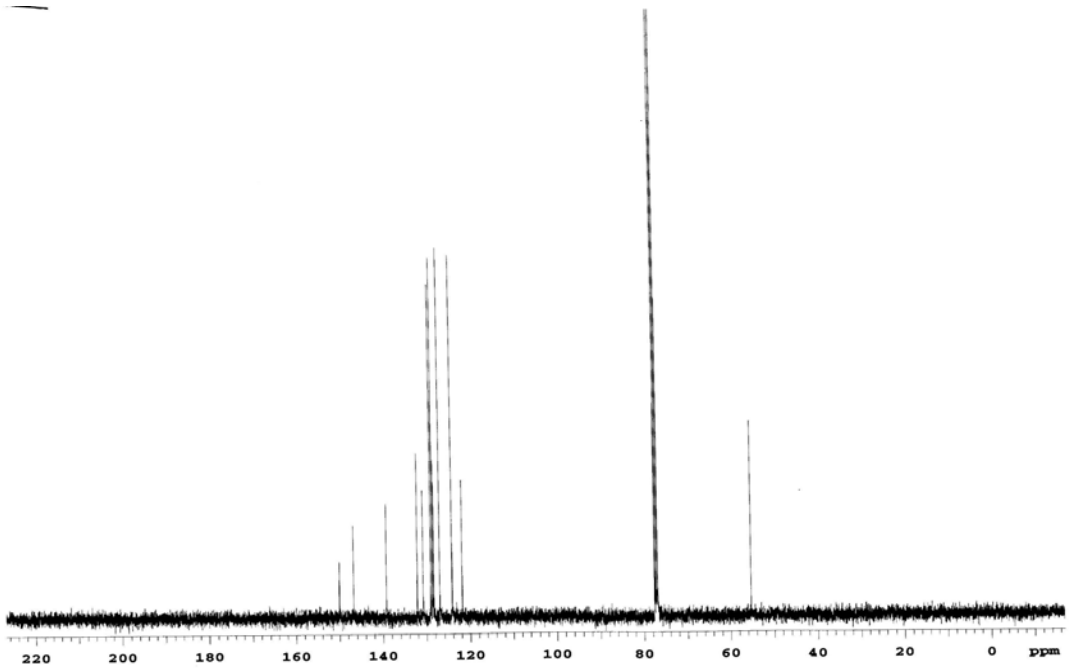
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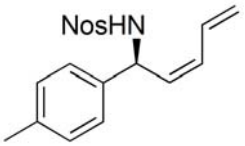
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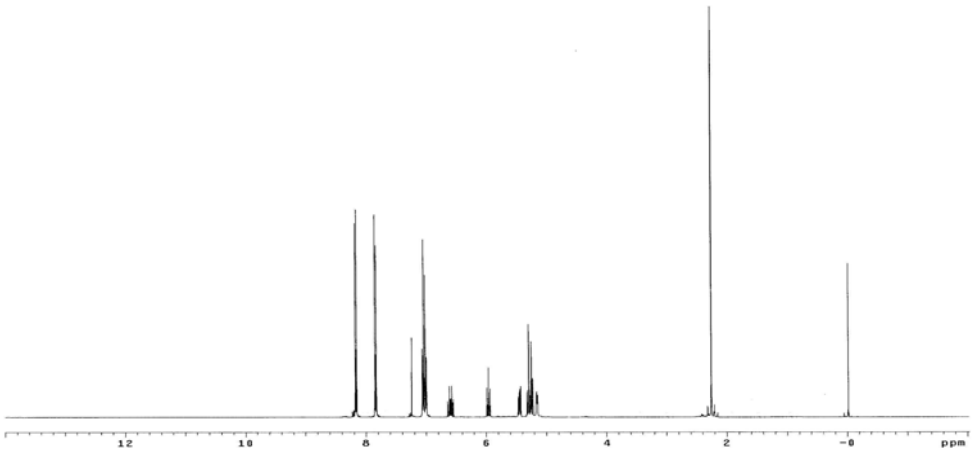
4.33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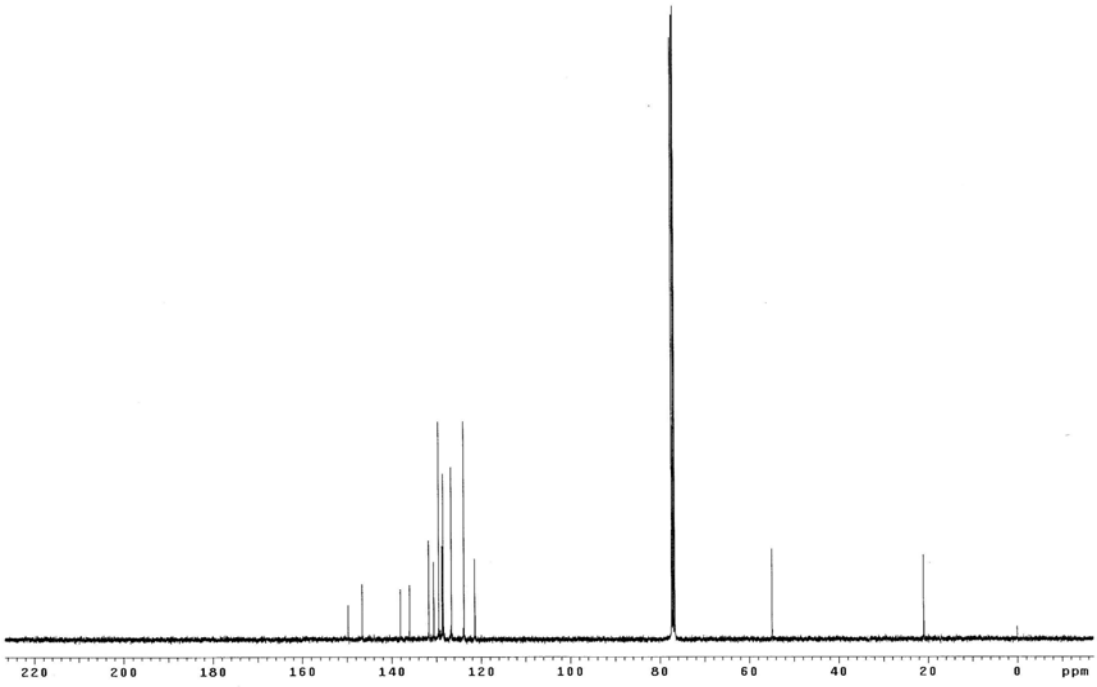
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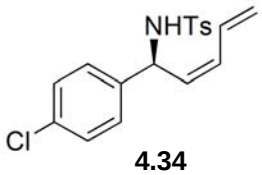
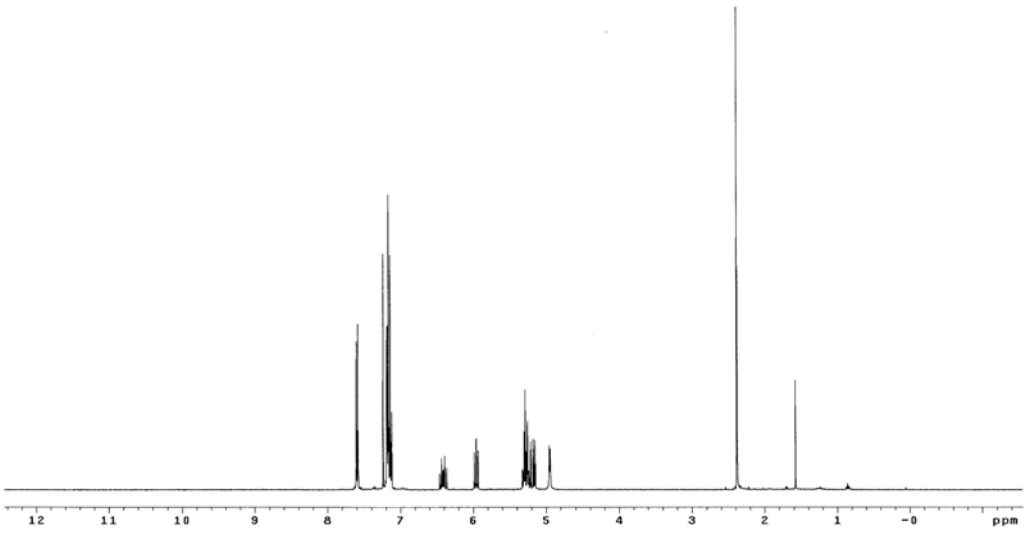

NHTs
Cl

4.34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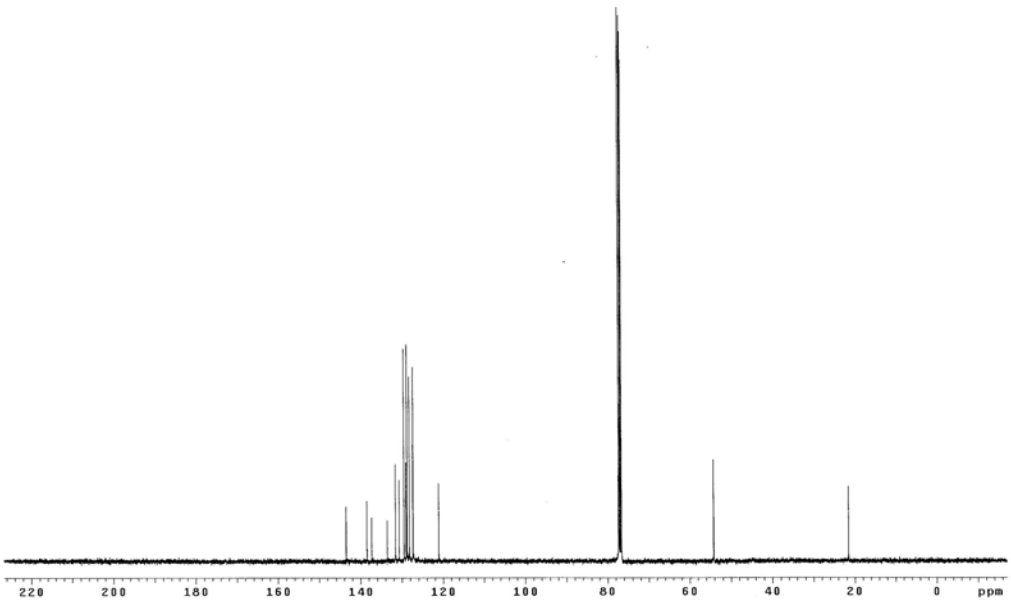
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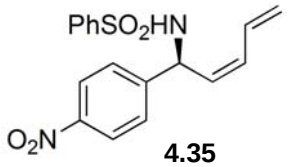
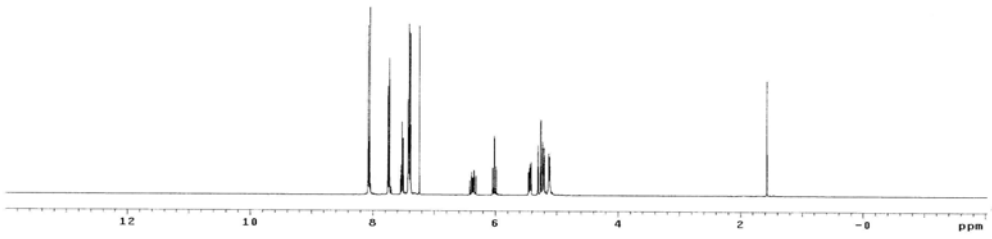

PhSO2HN
O2N

4.35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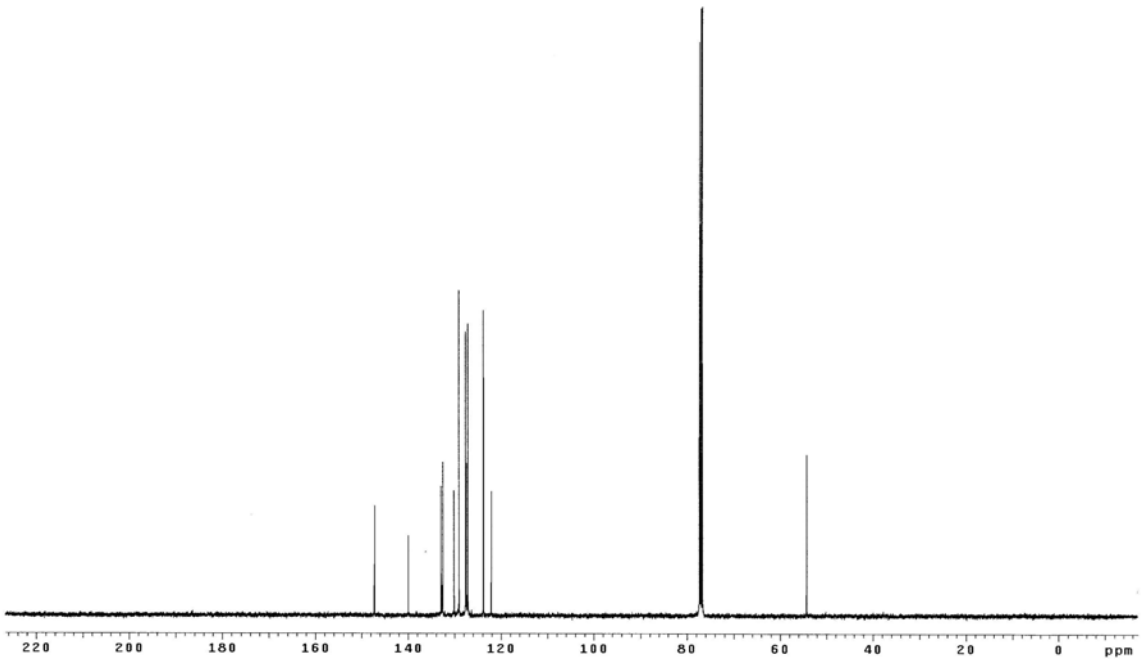
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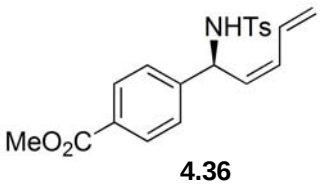
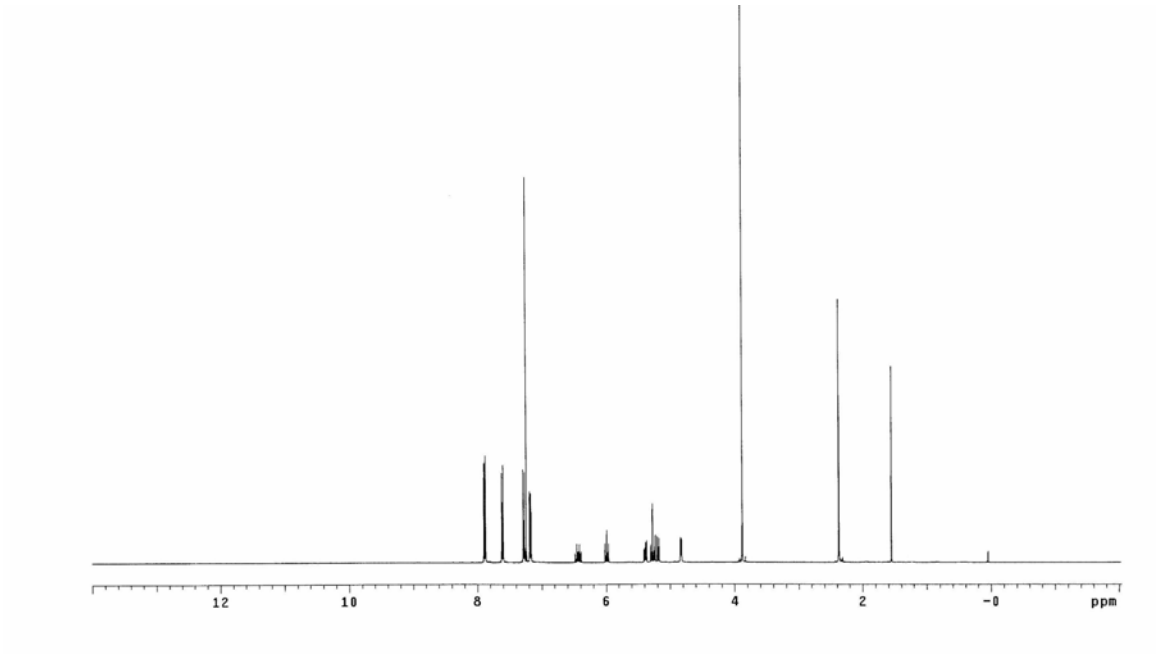

NHTs
MeO2C

4.36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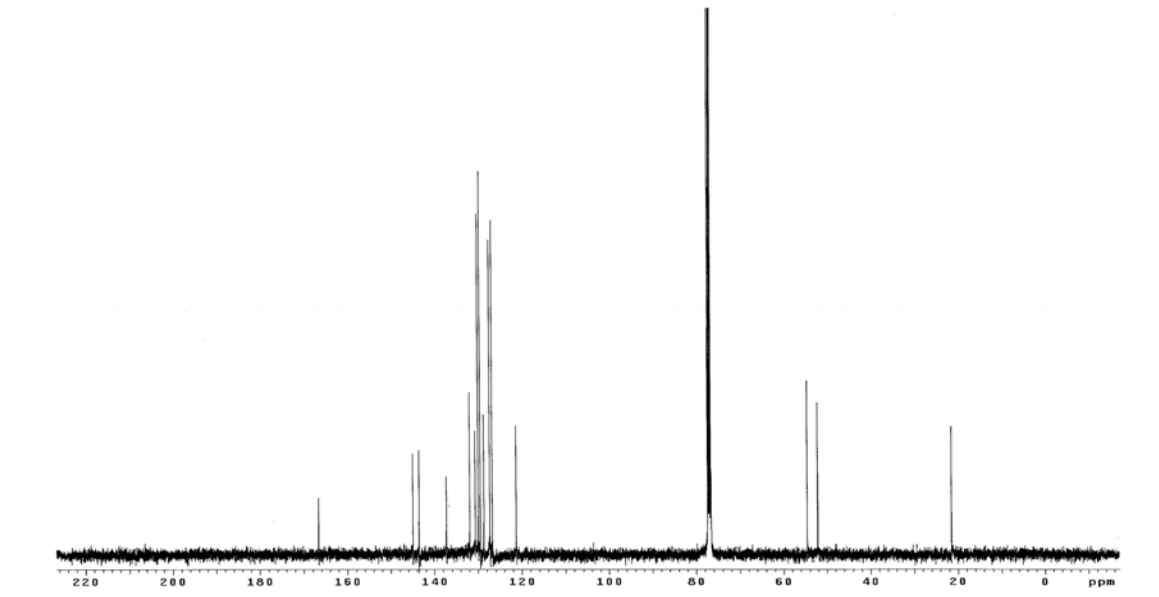
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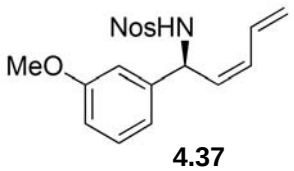
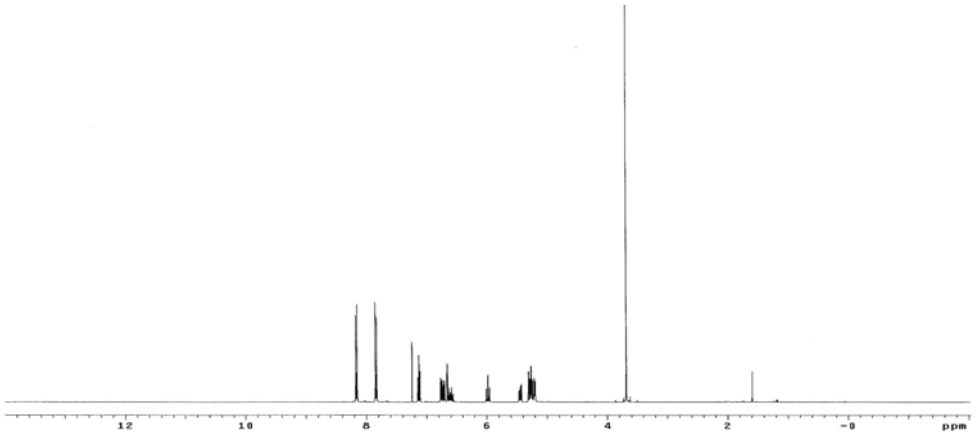

NosHN
MeO

4.37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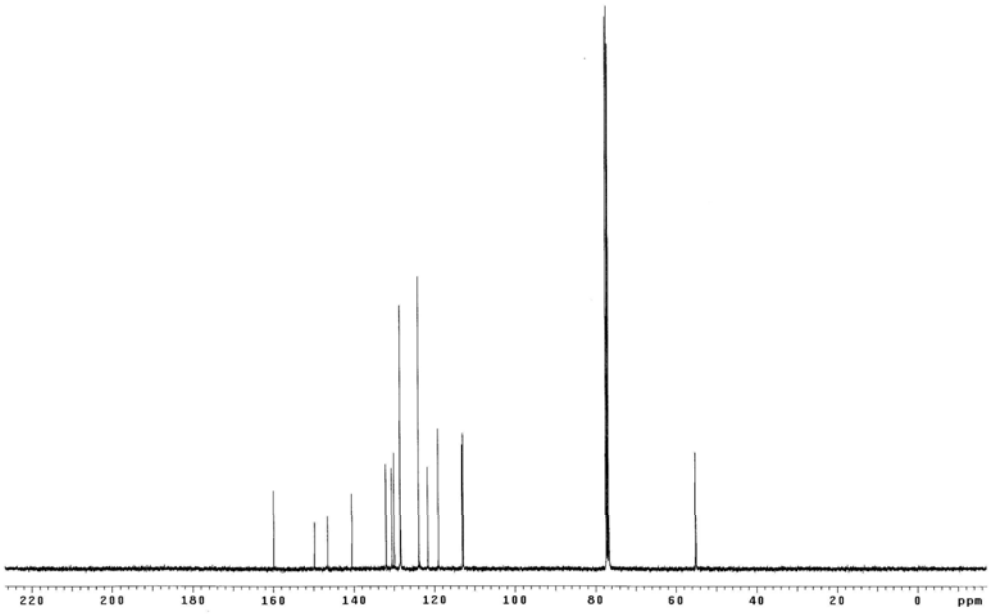
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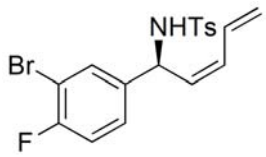
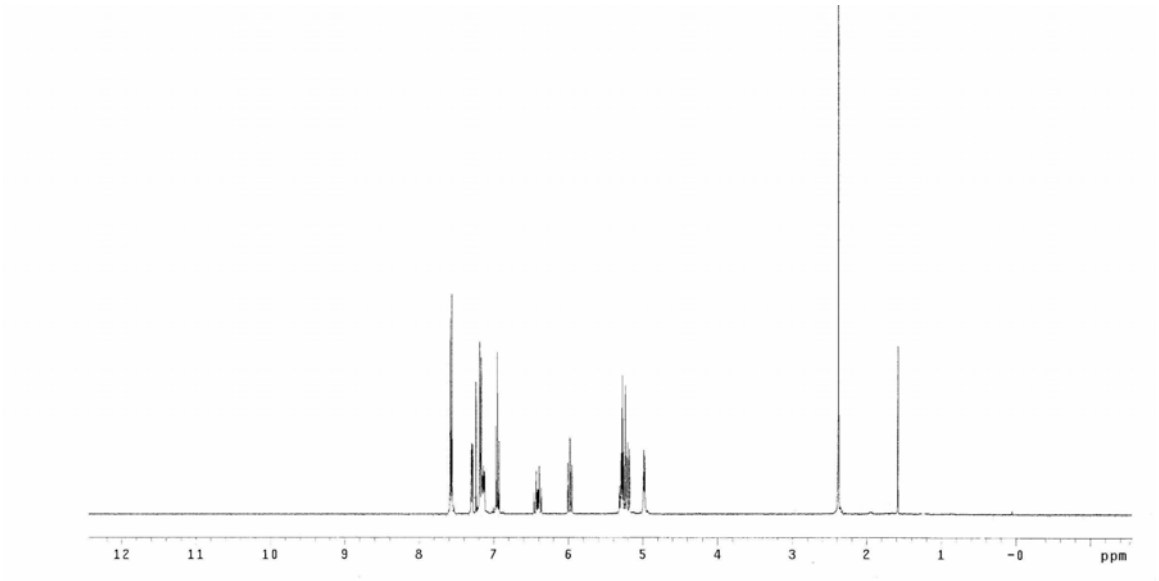

NHTs
Br
F

4.38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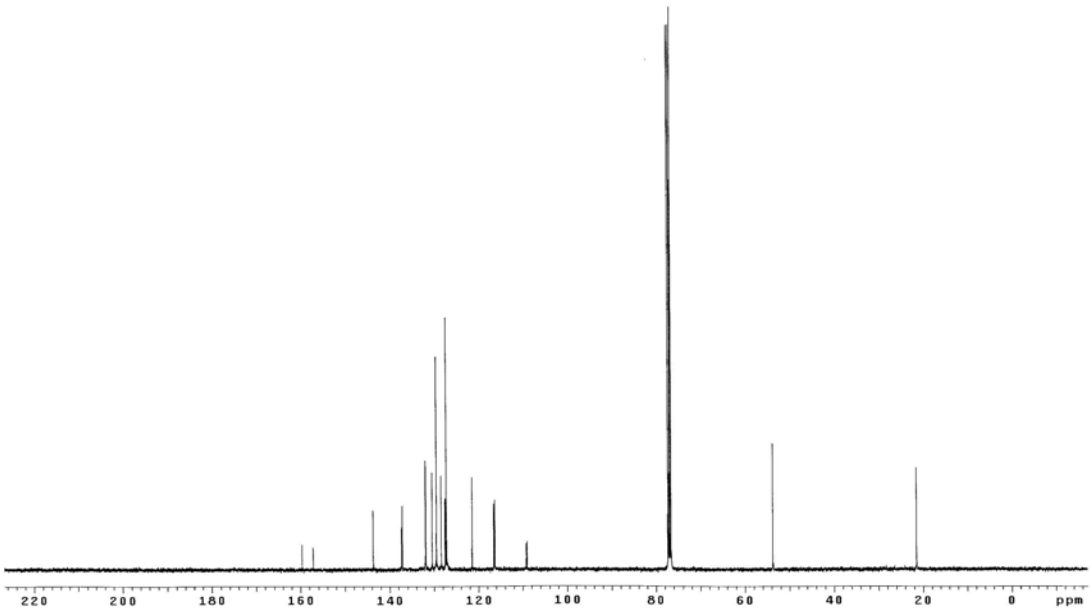
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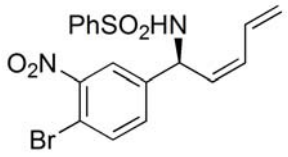
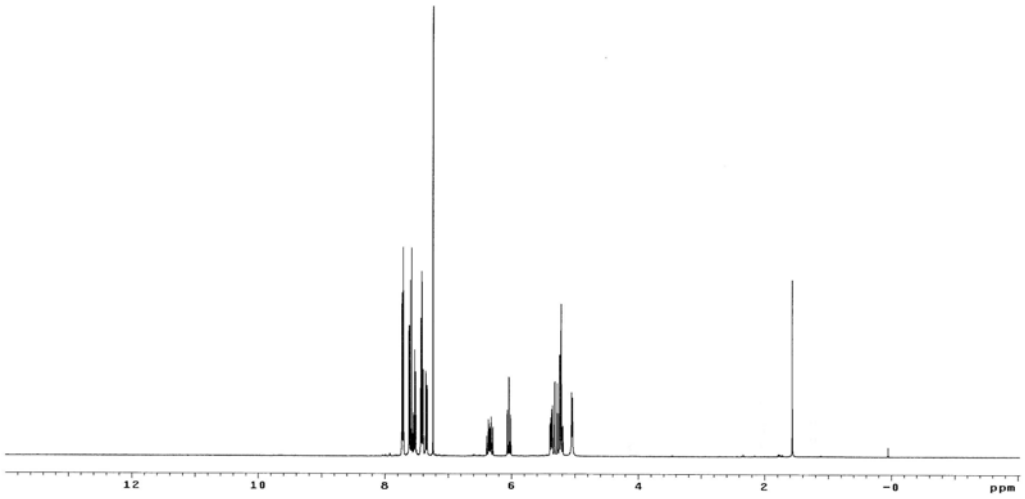

PhSO2HN
O2N
Br

4.39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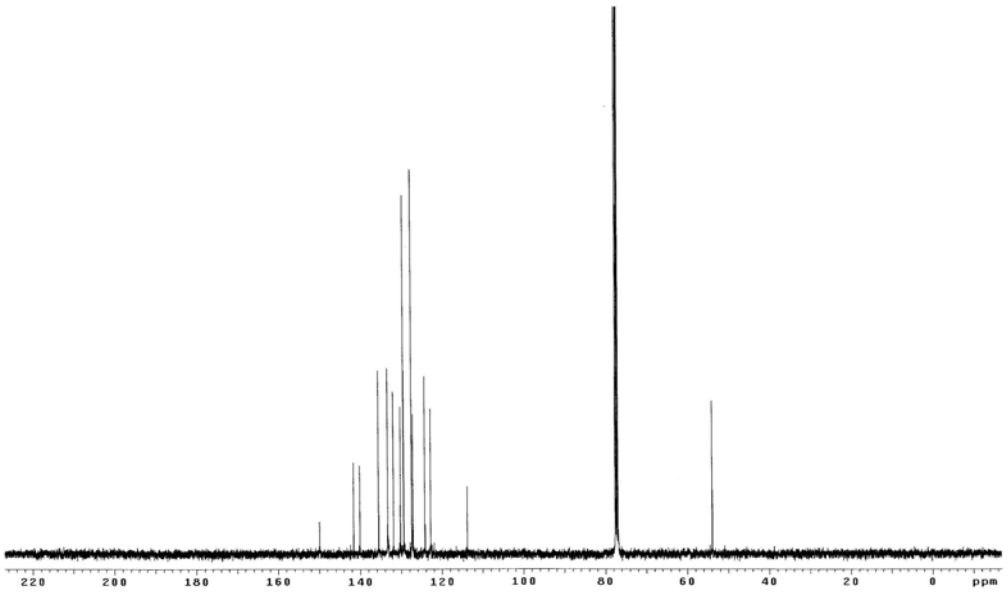
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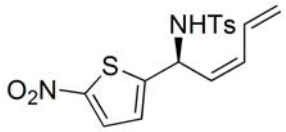
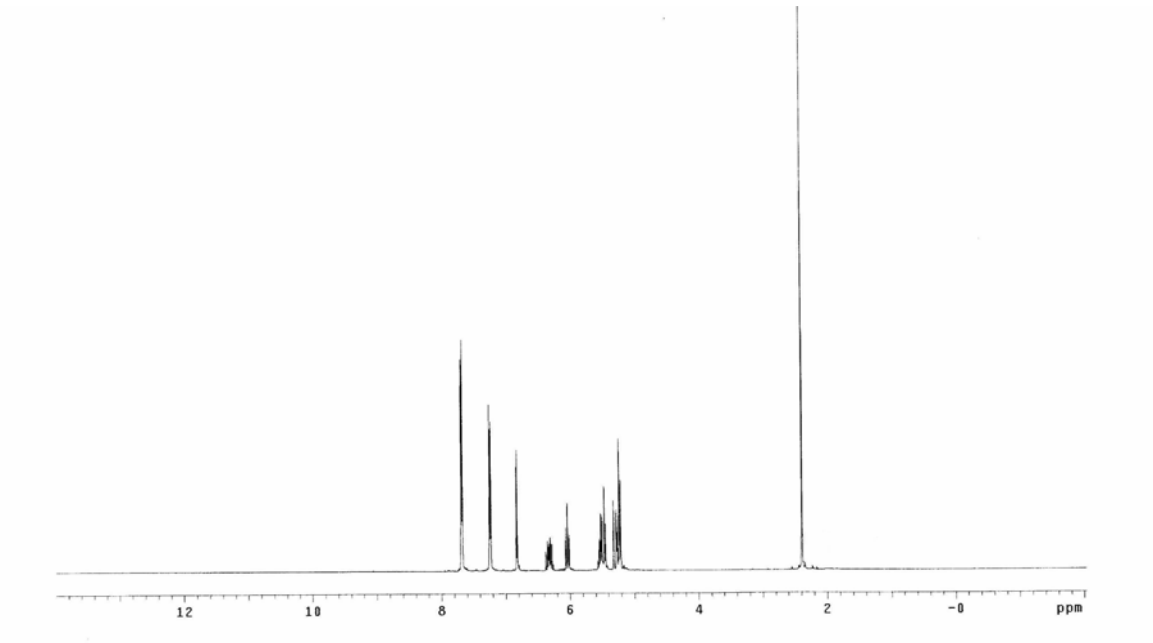

NHTs
S
O_2N

4.40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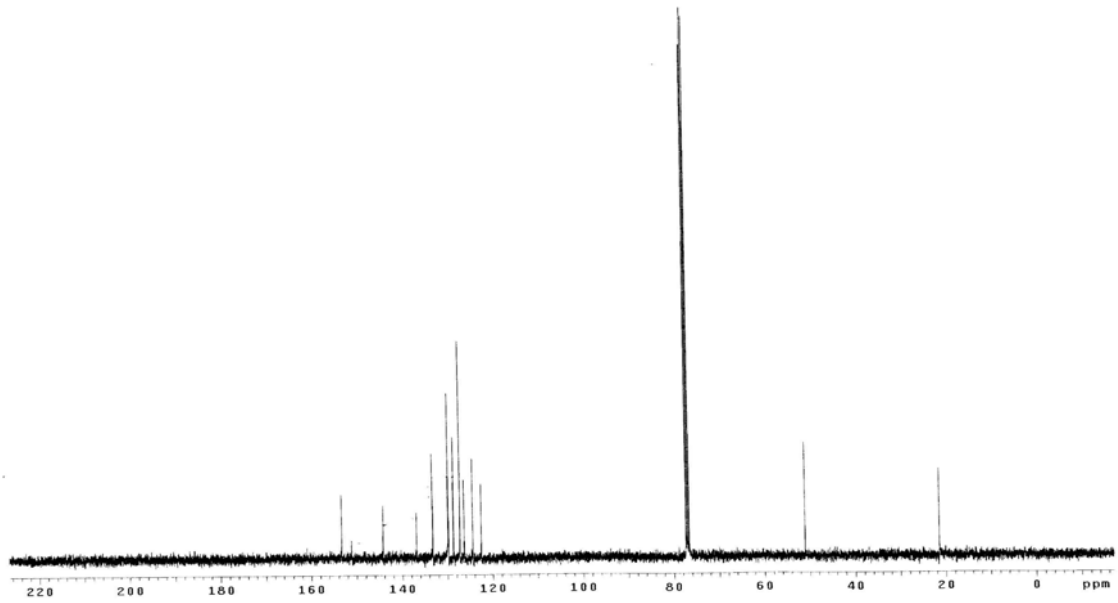
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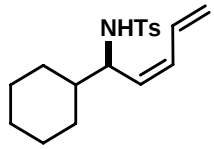

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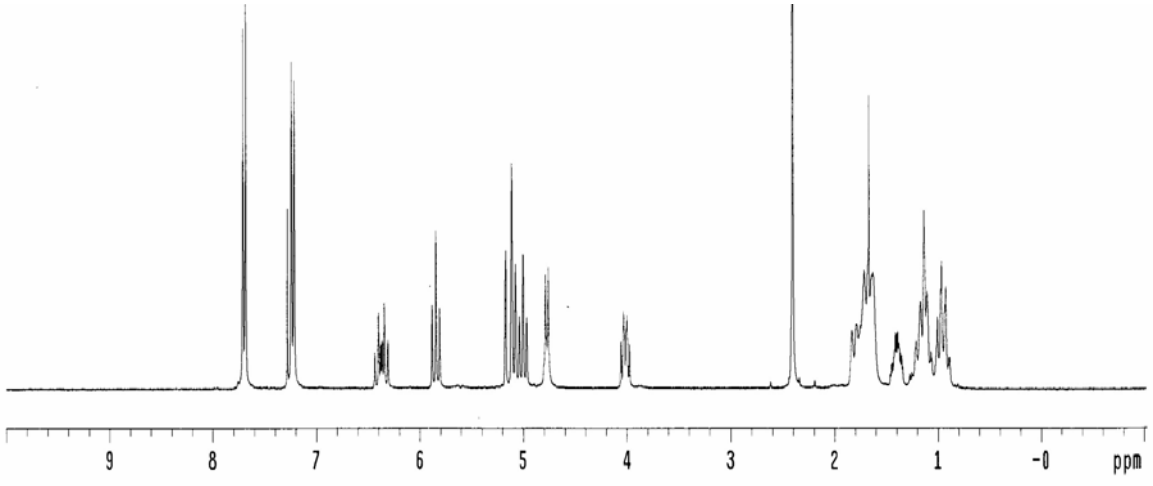

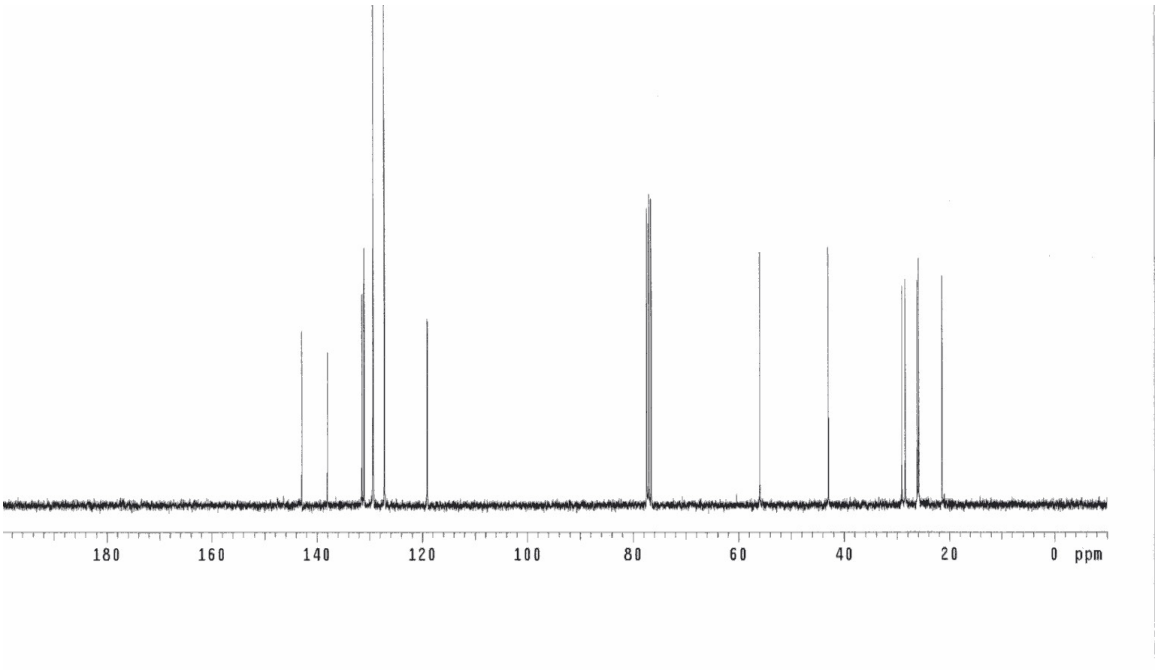

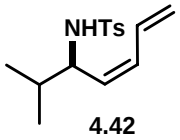

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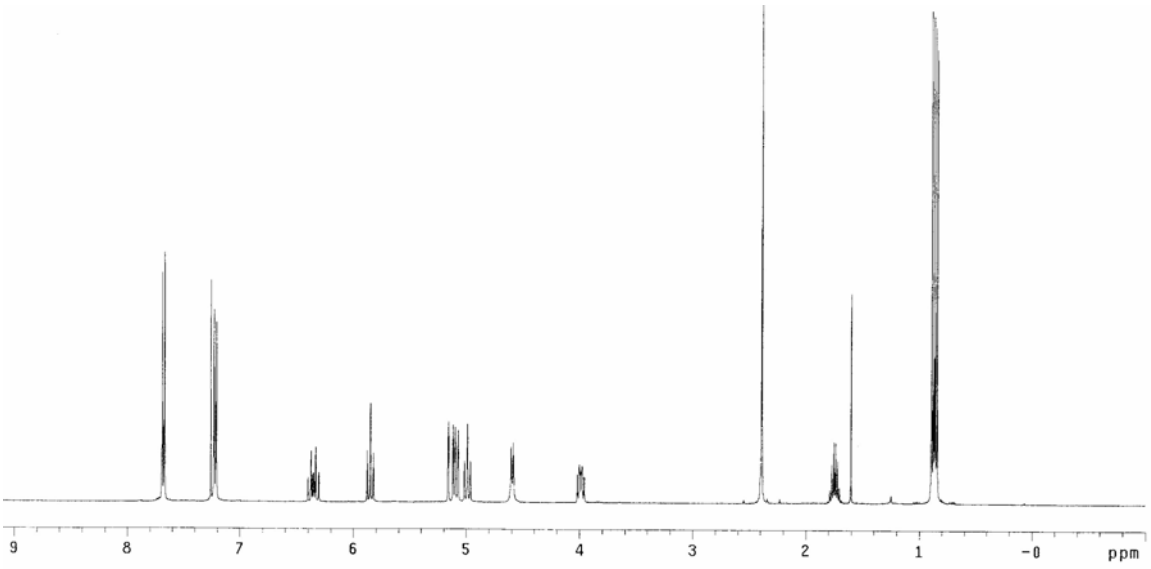

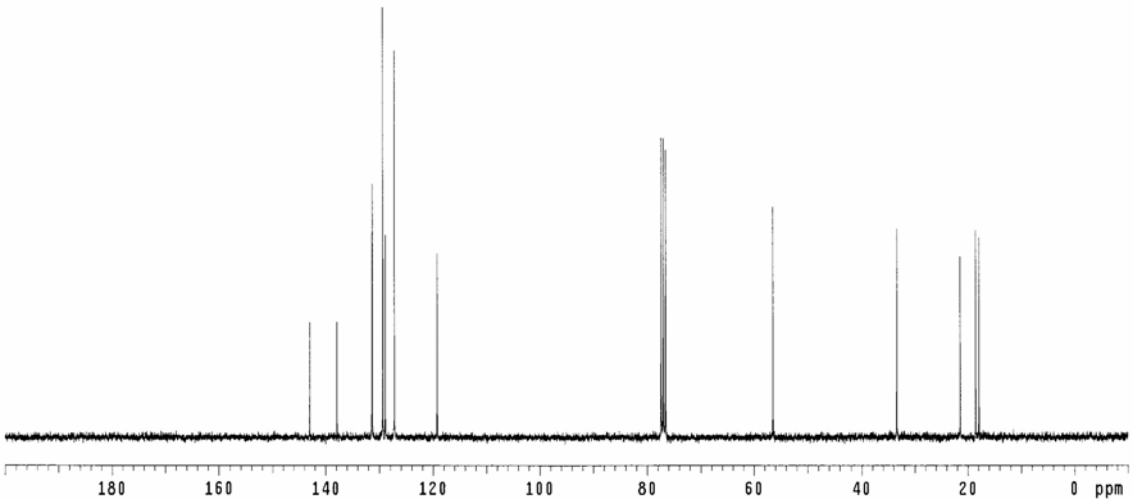

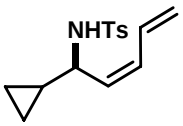

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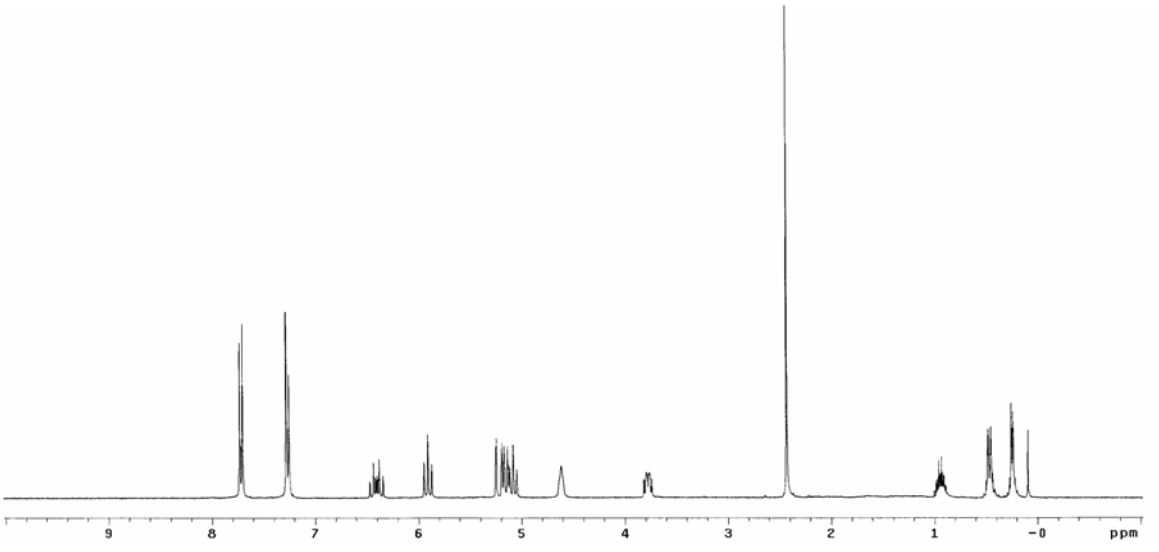

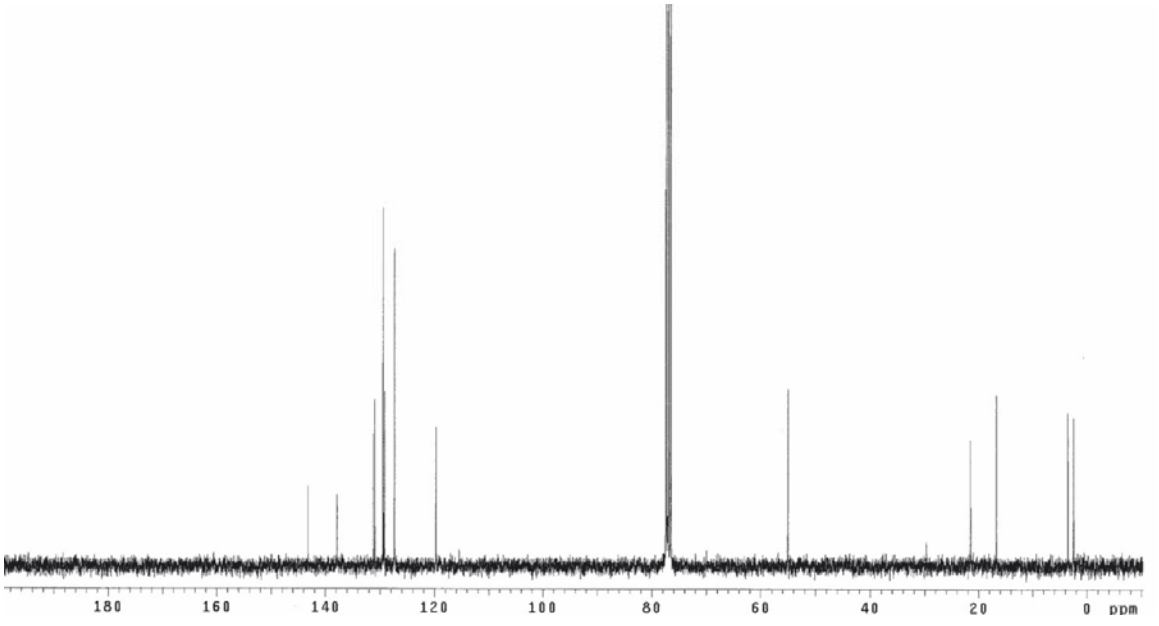

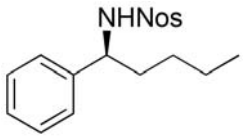
NHNos

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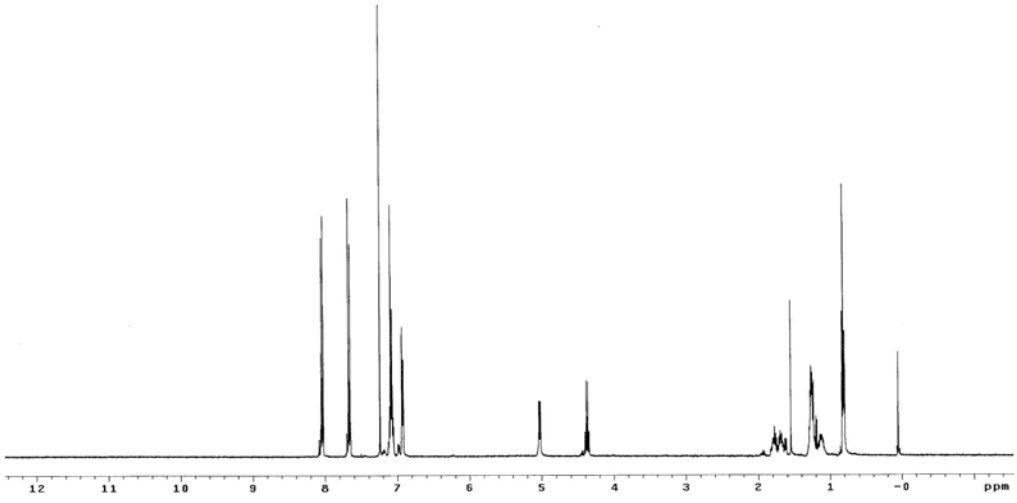
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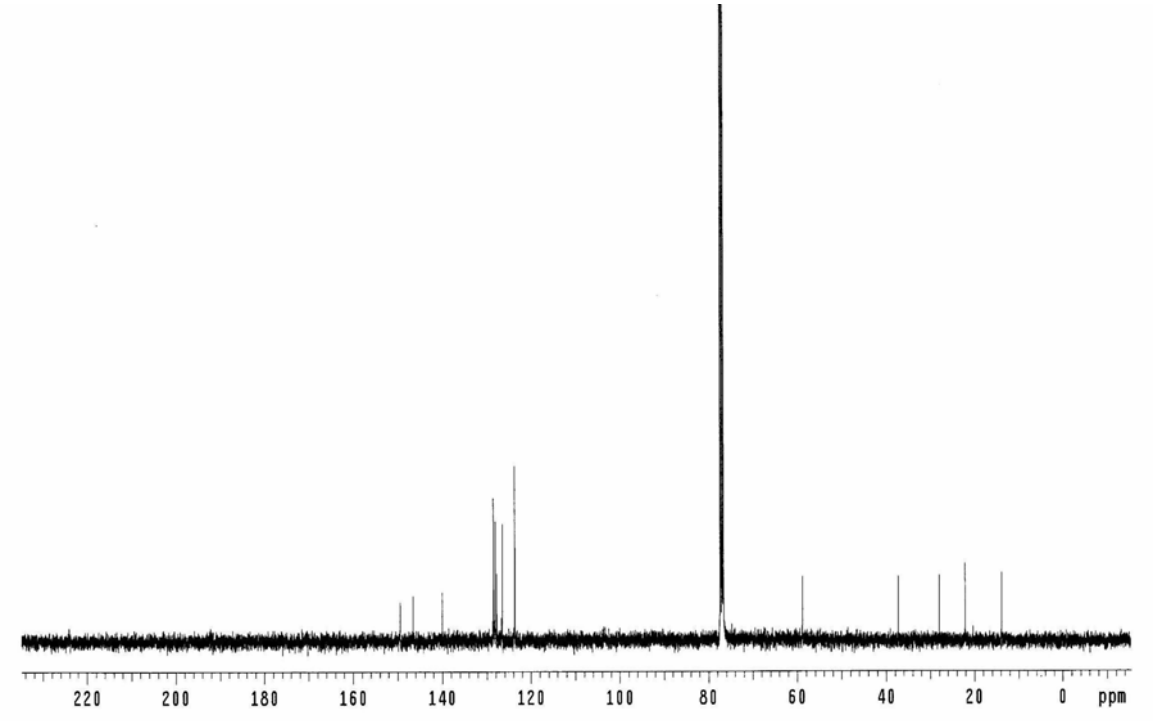
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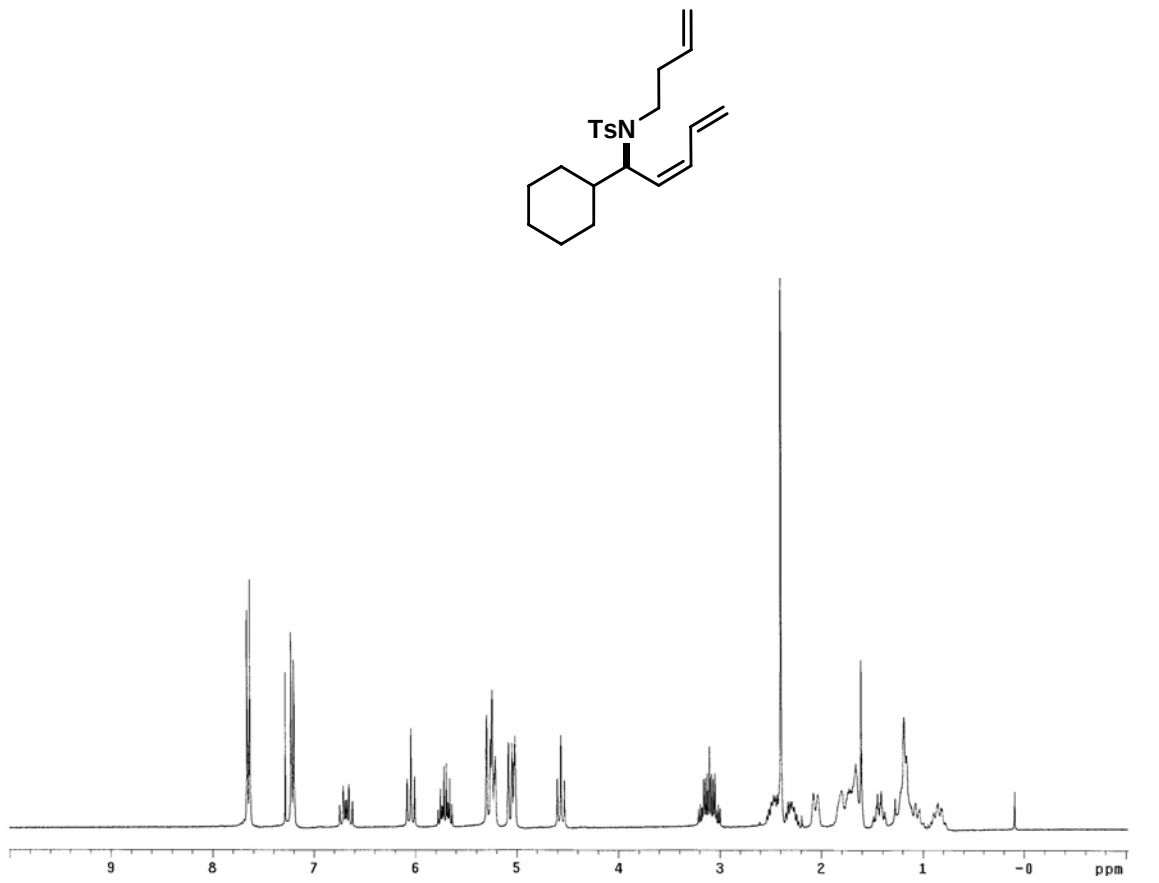
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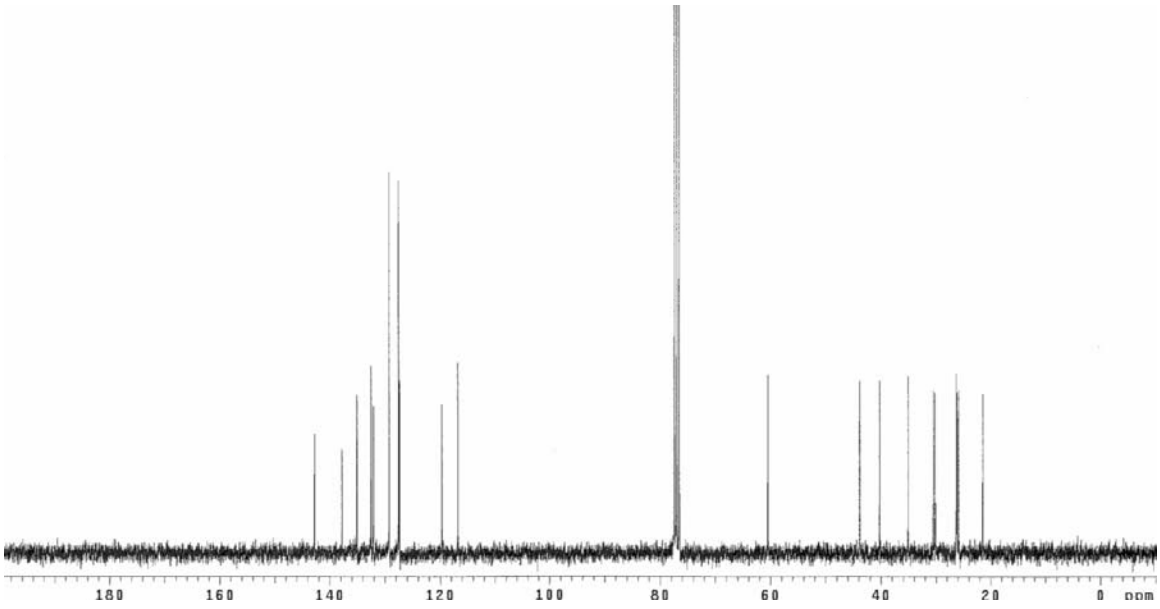
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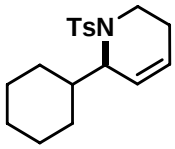

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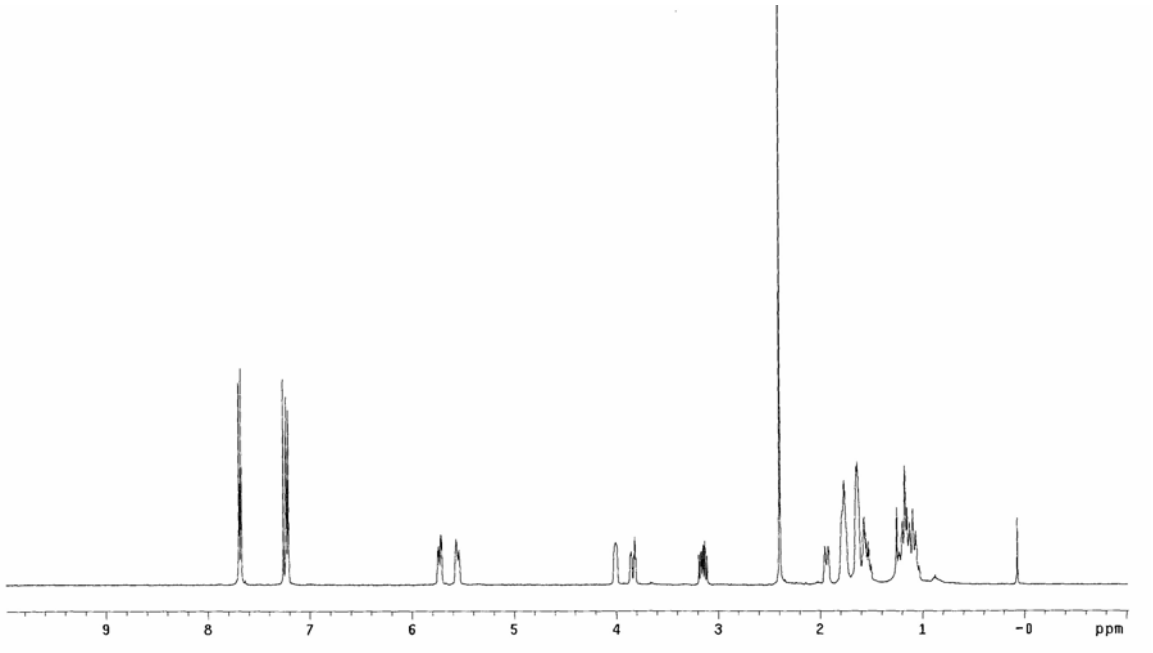

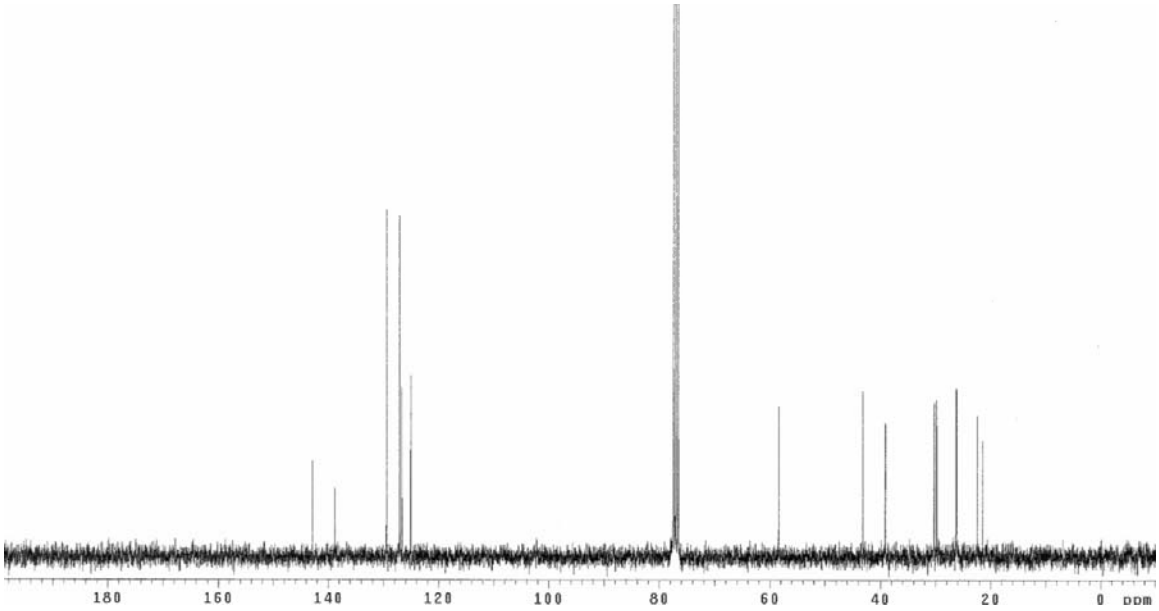

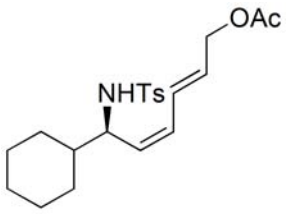
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NHTs

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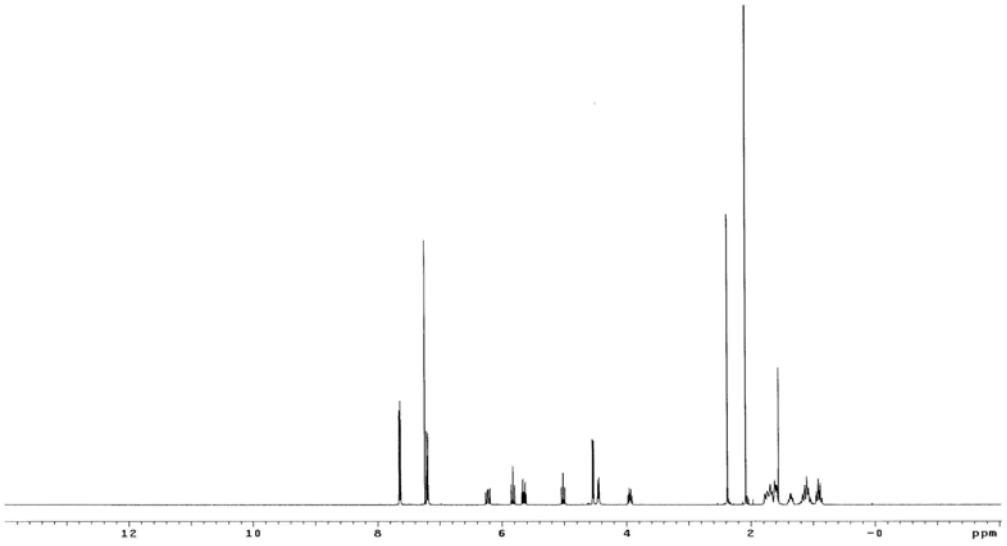
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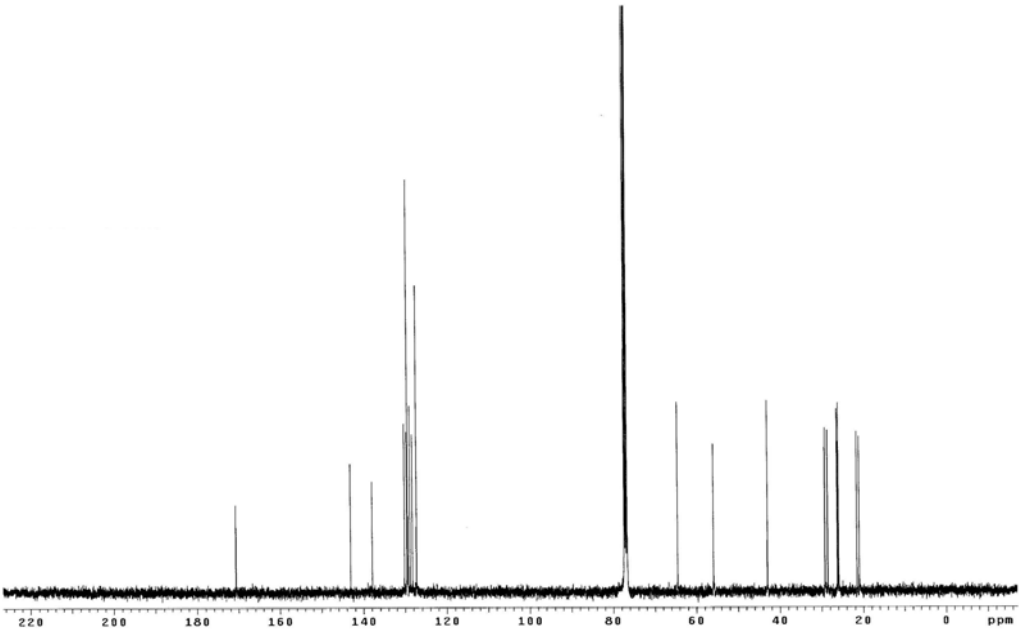
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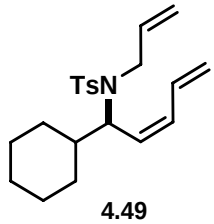

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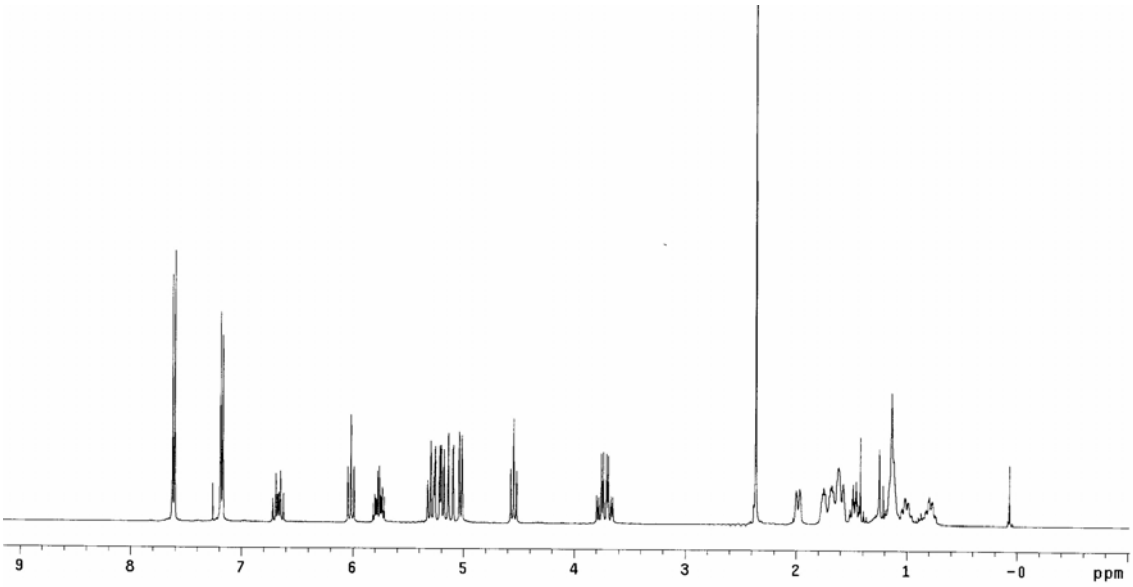

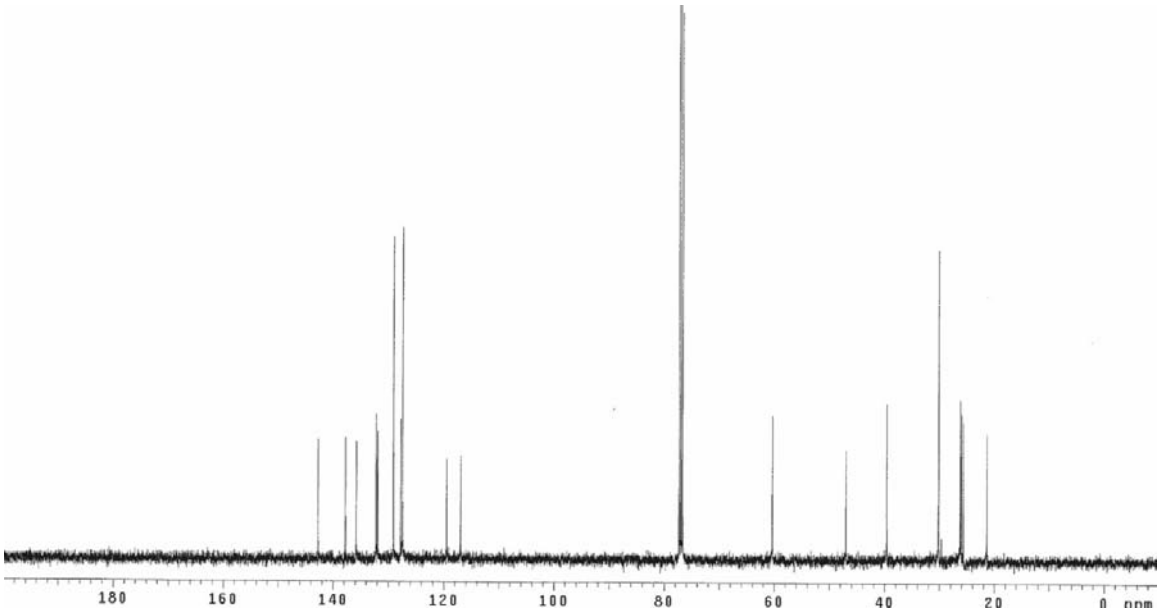

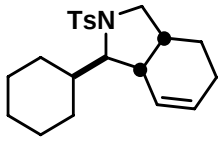

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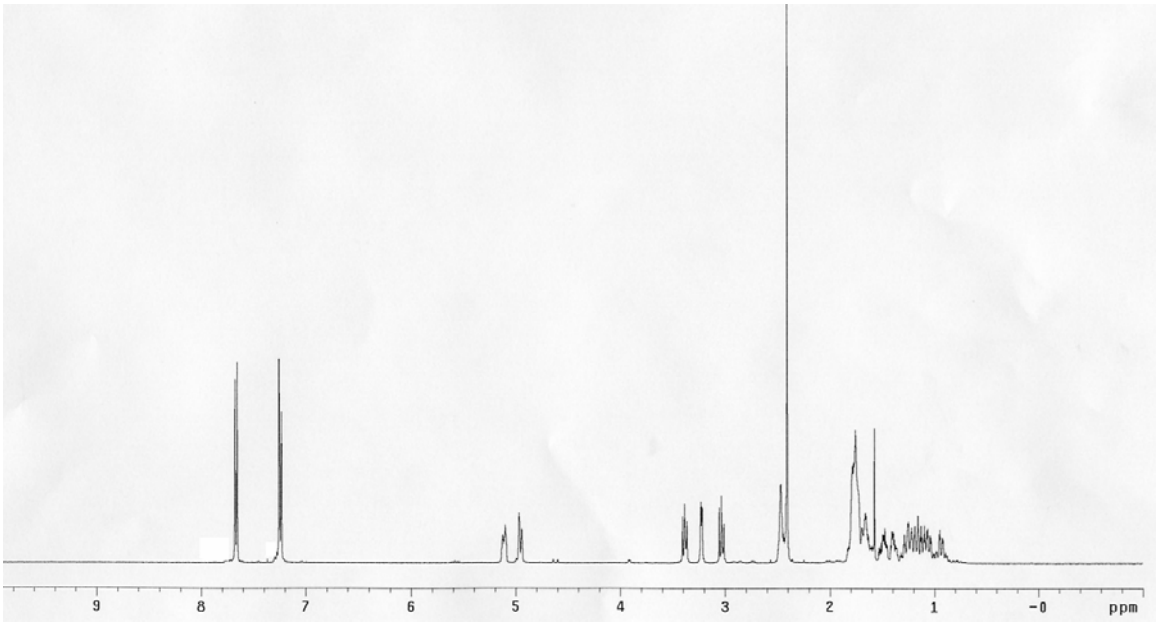
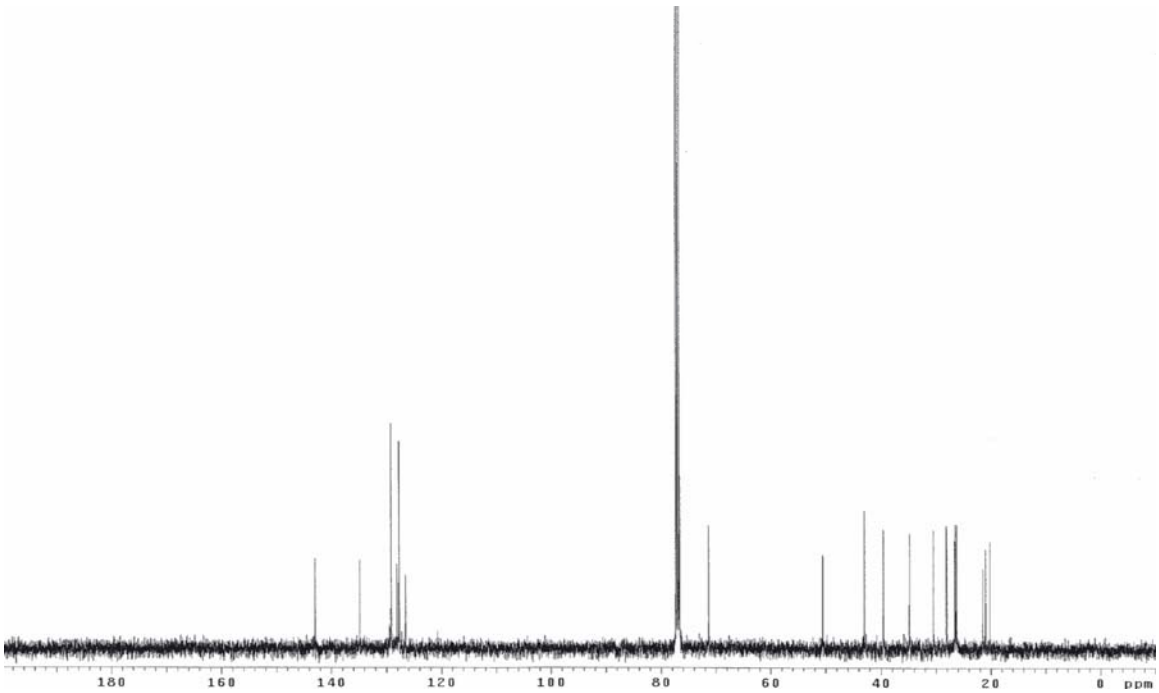
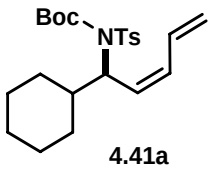
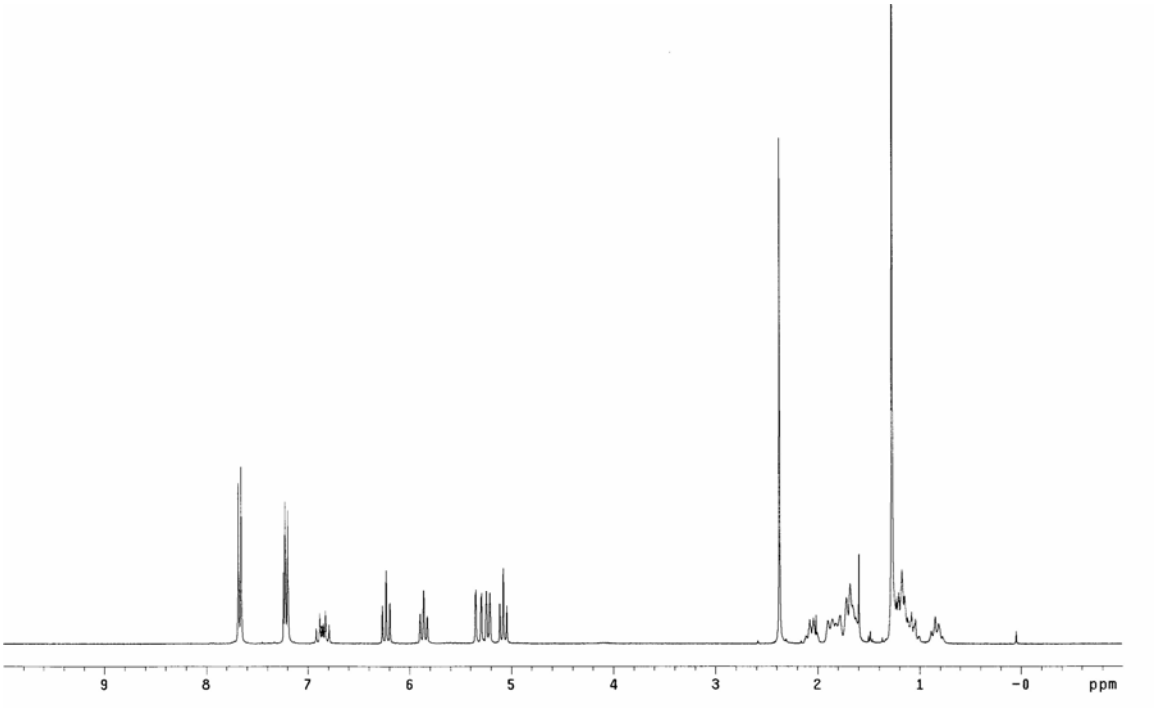
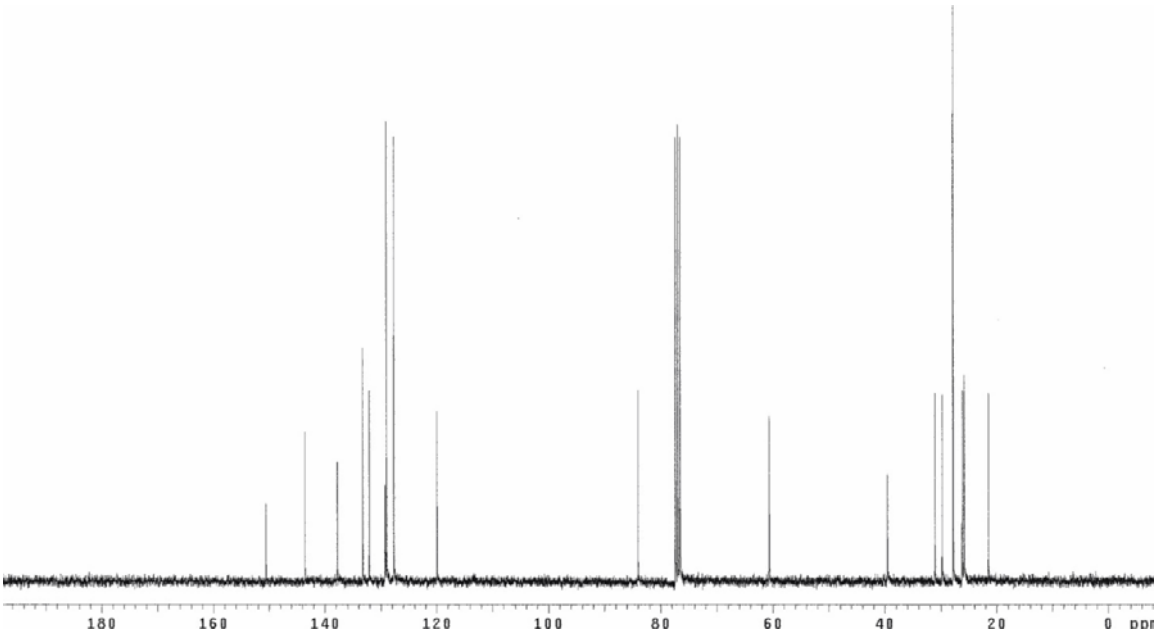


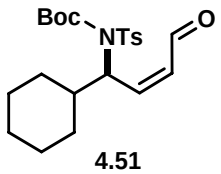




4.41a



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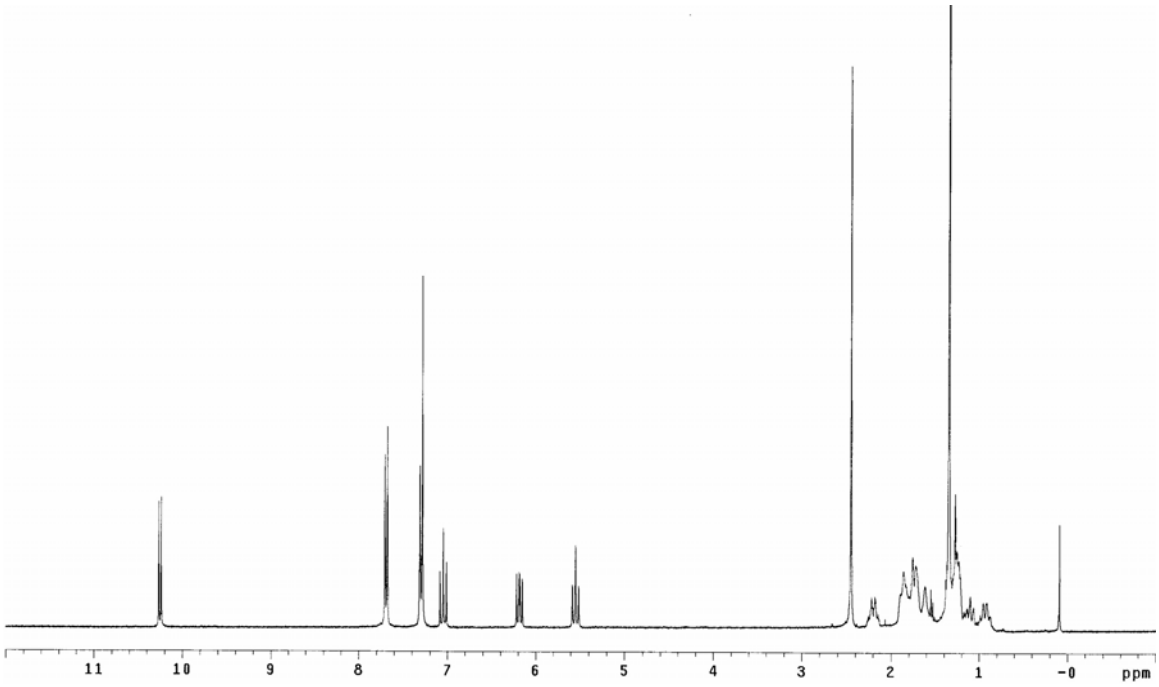
4.51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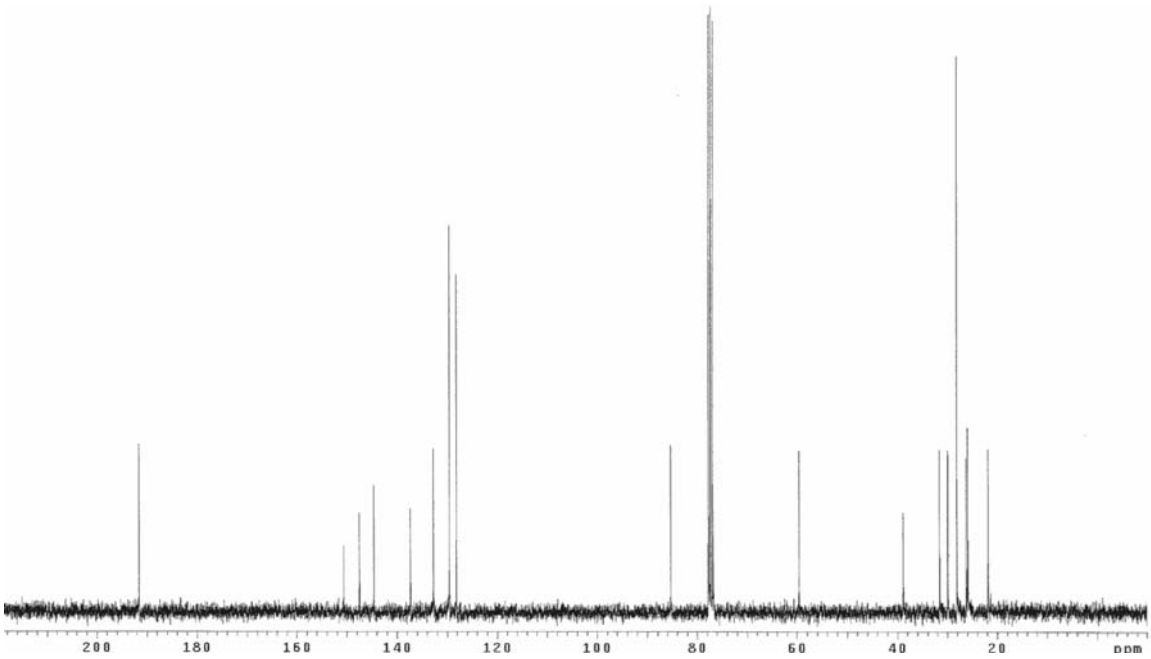
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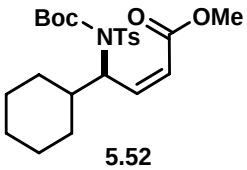
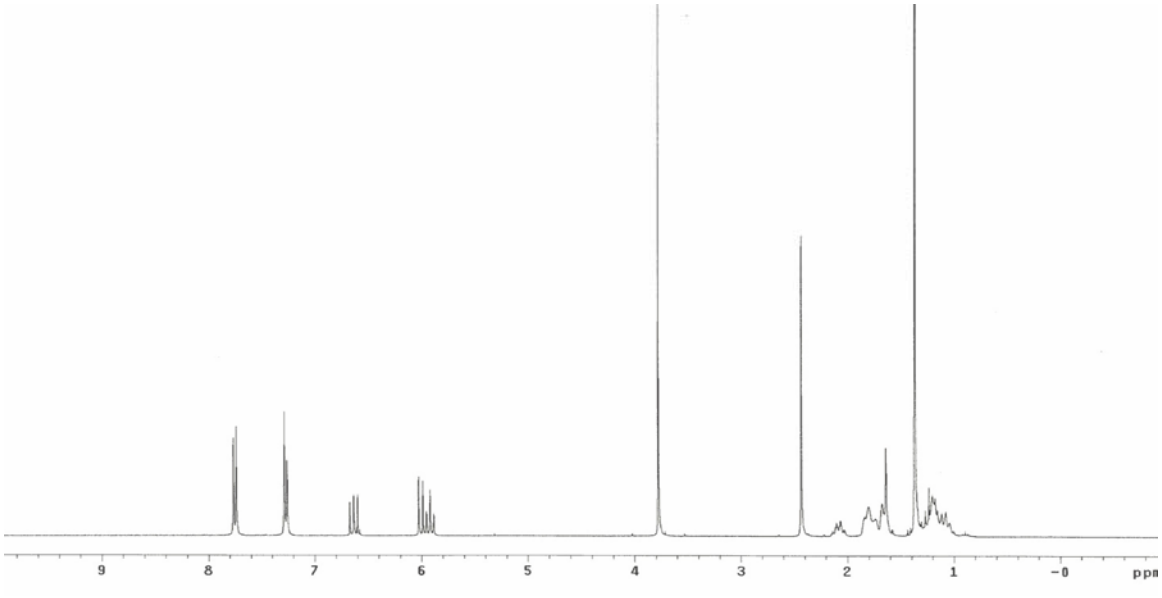

Boc
NTs
O
OMe

5.52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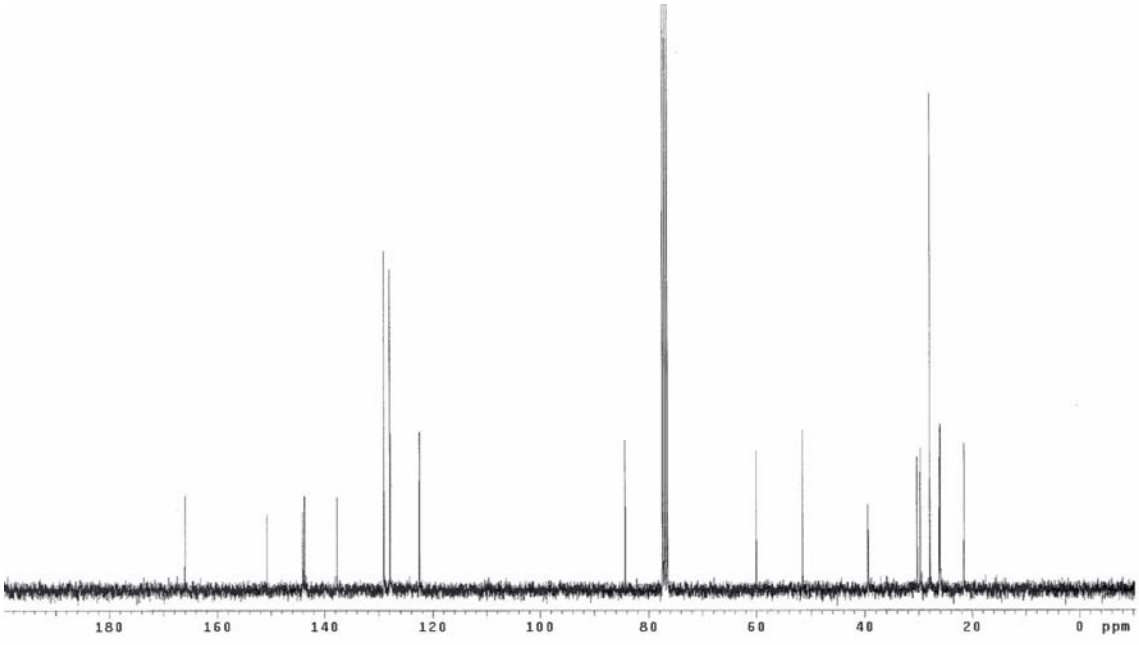
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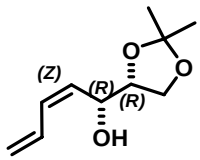
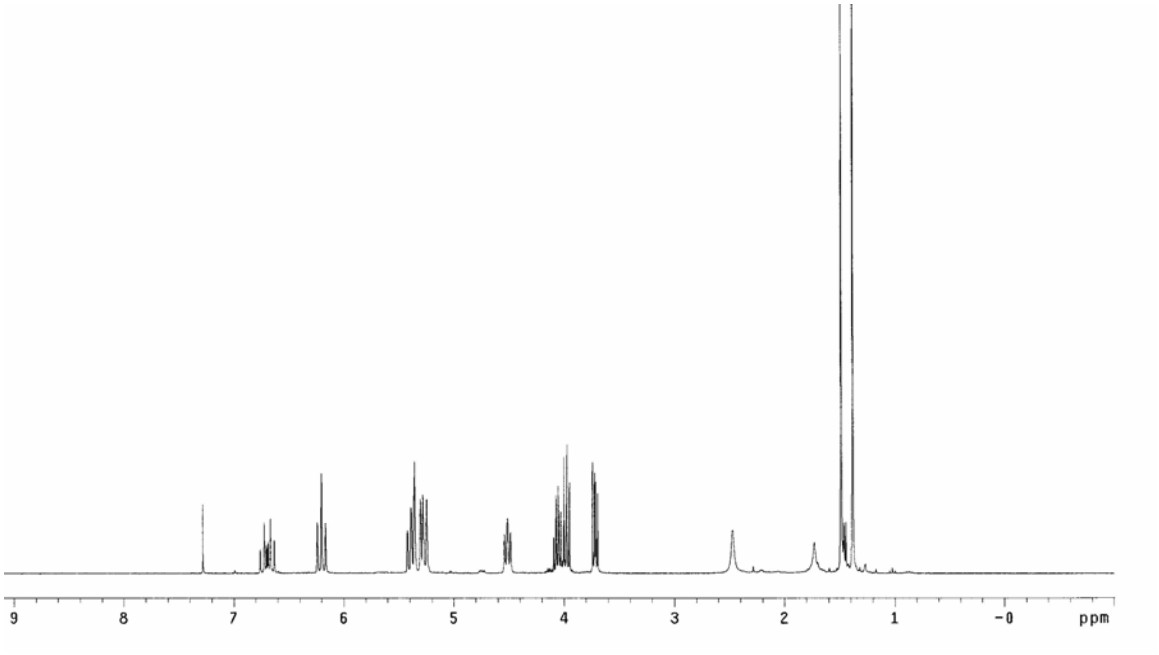
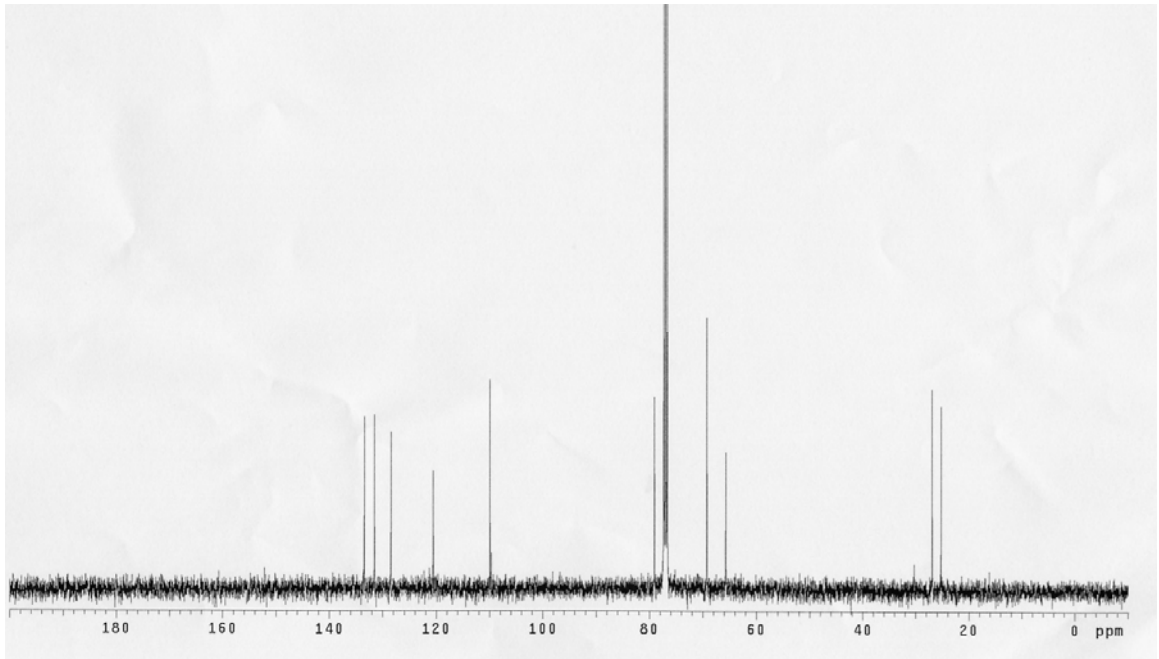
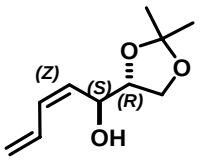


***syn*-4.58**







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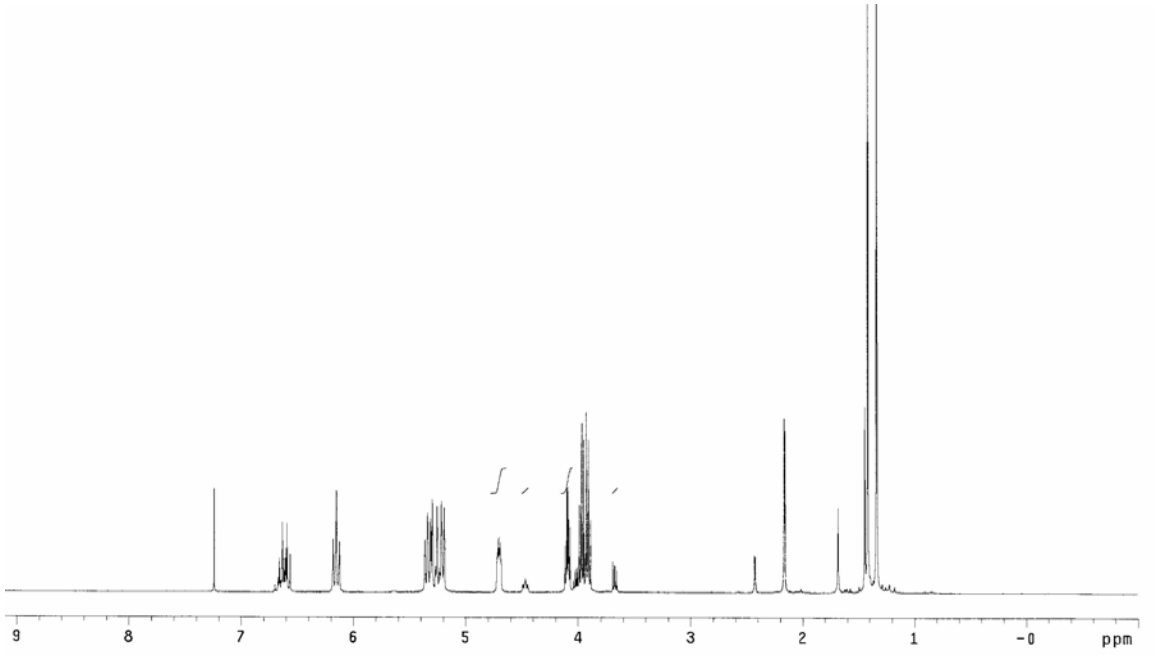

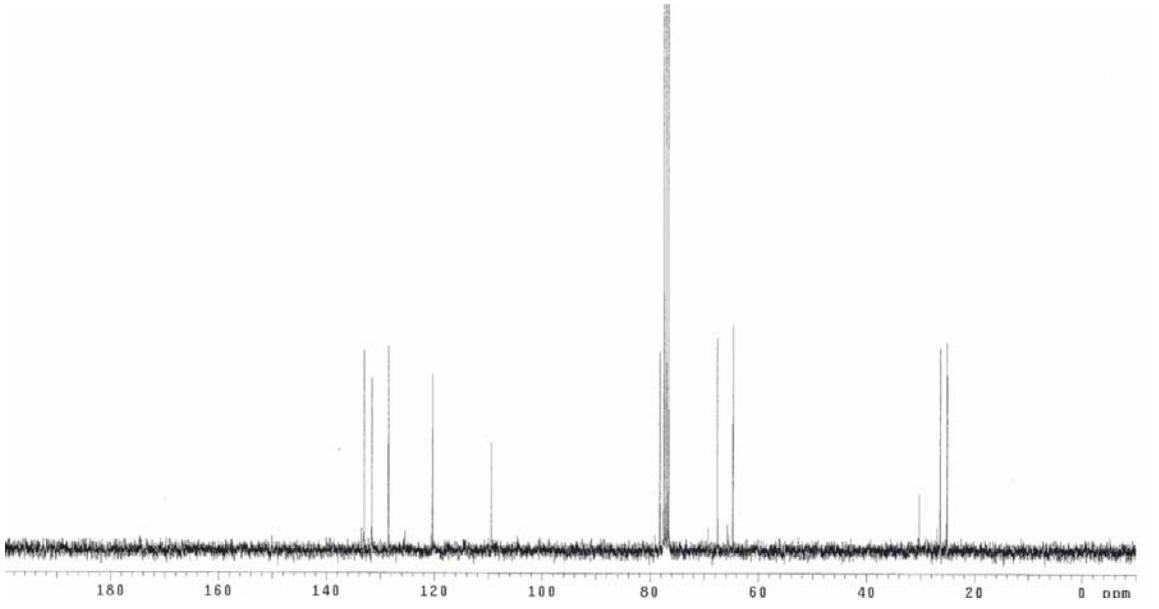

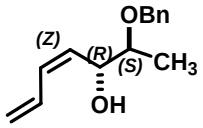

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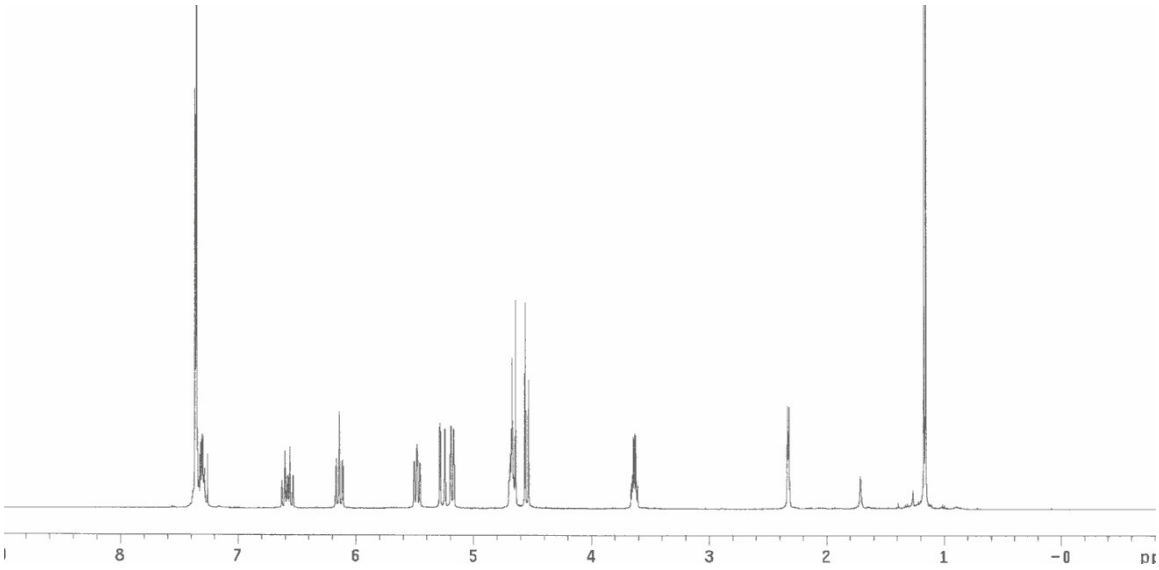
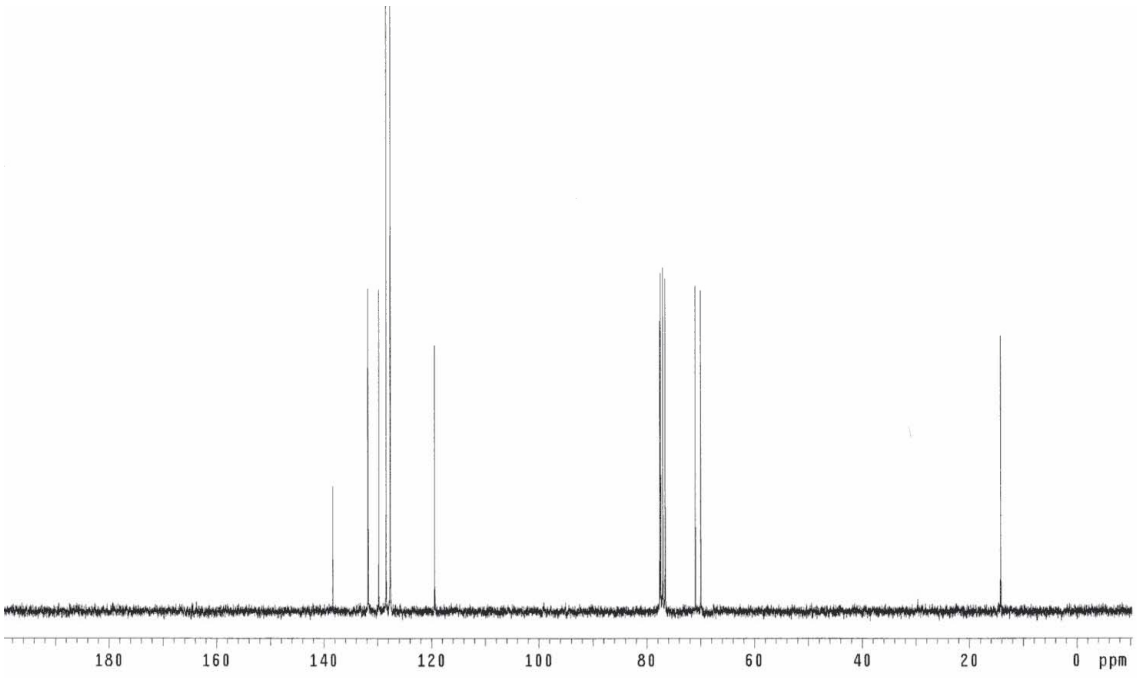
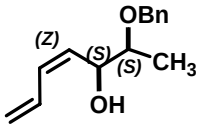
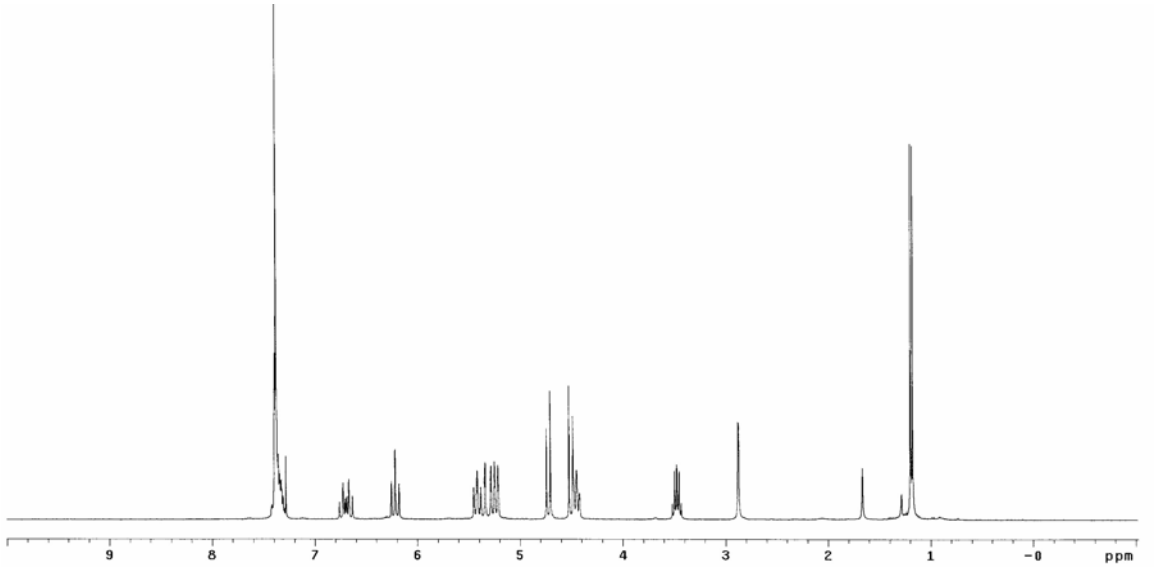





OBn
(Z)
(S)
(S)
CH3
OH

***syn*-4.62**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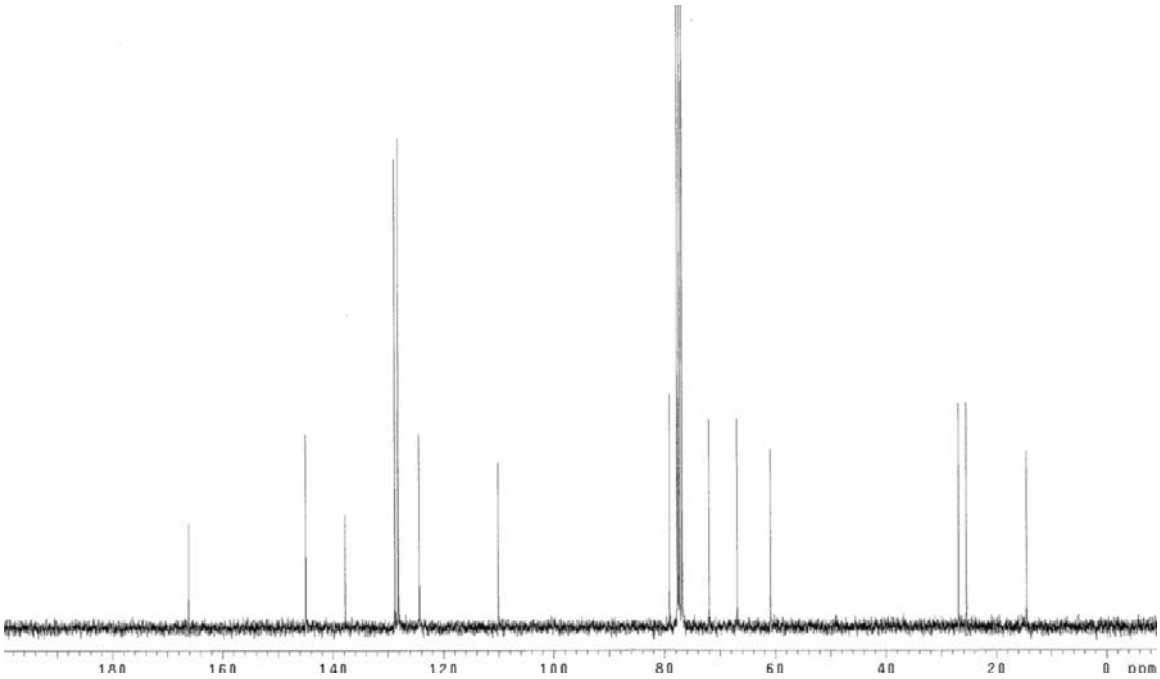
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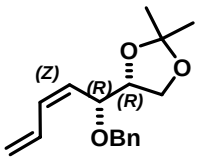

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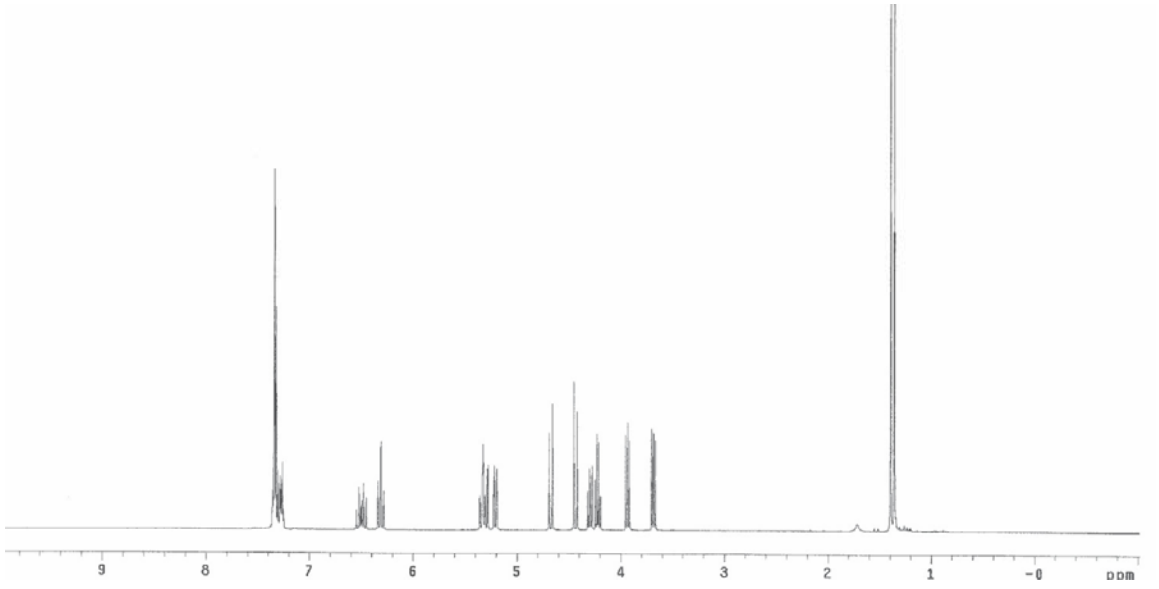

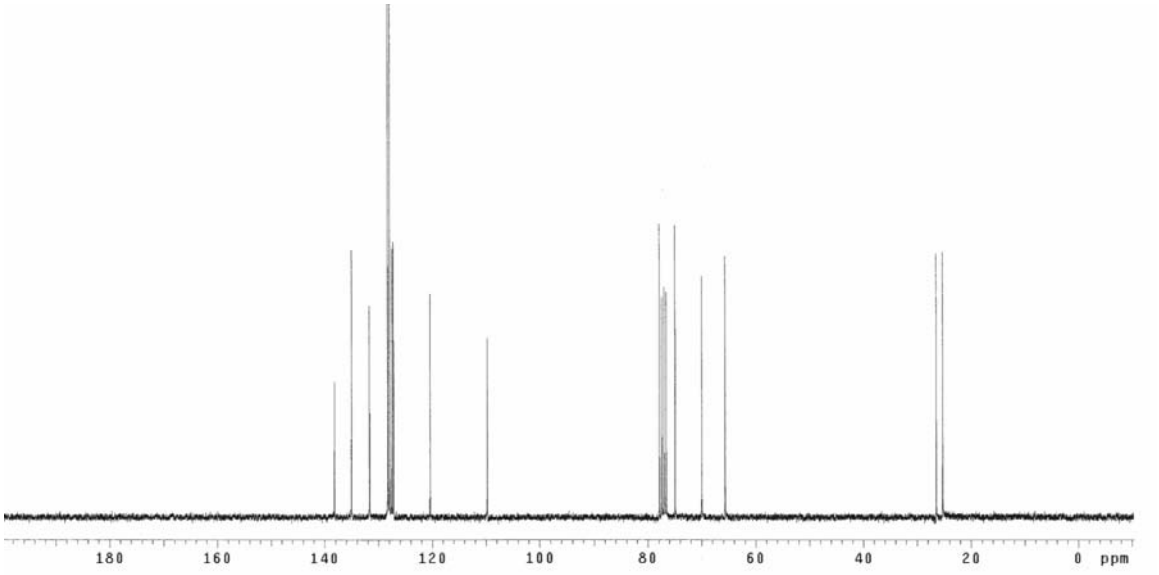

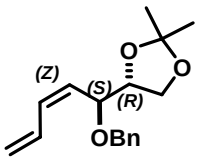

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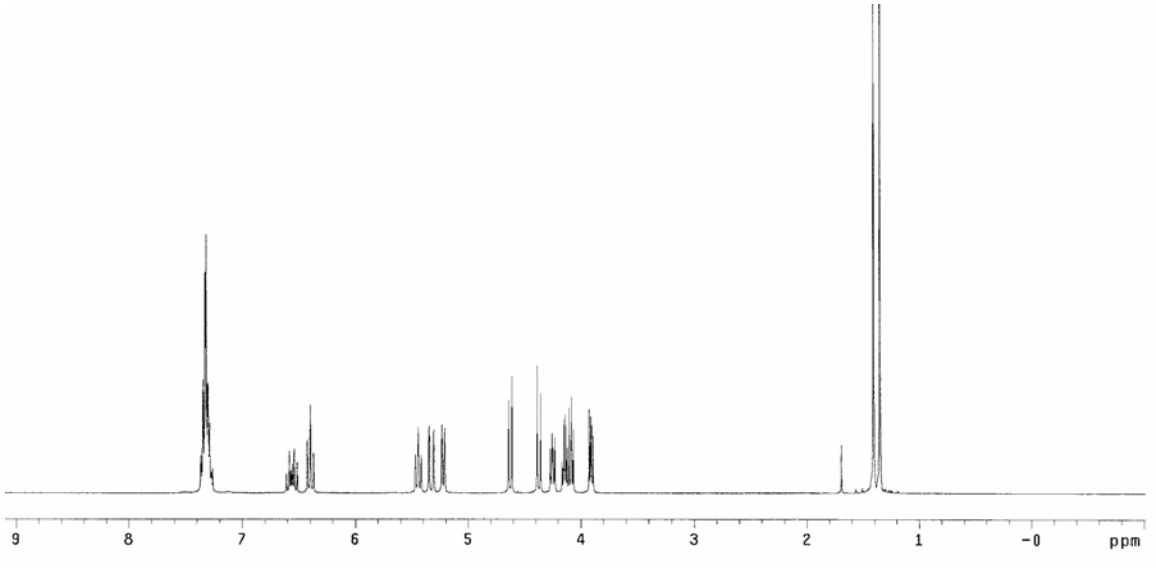

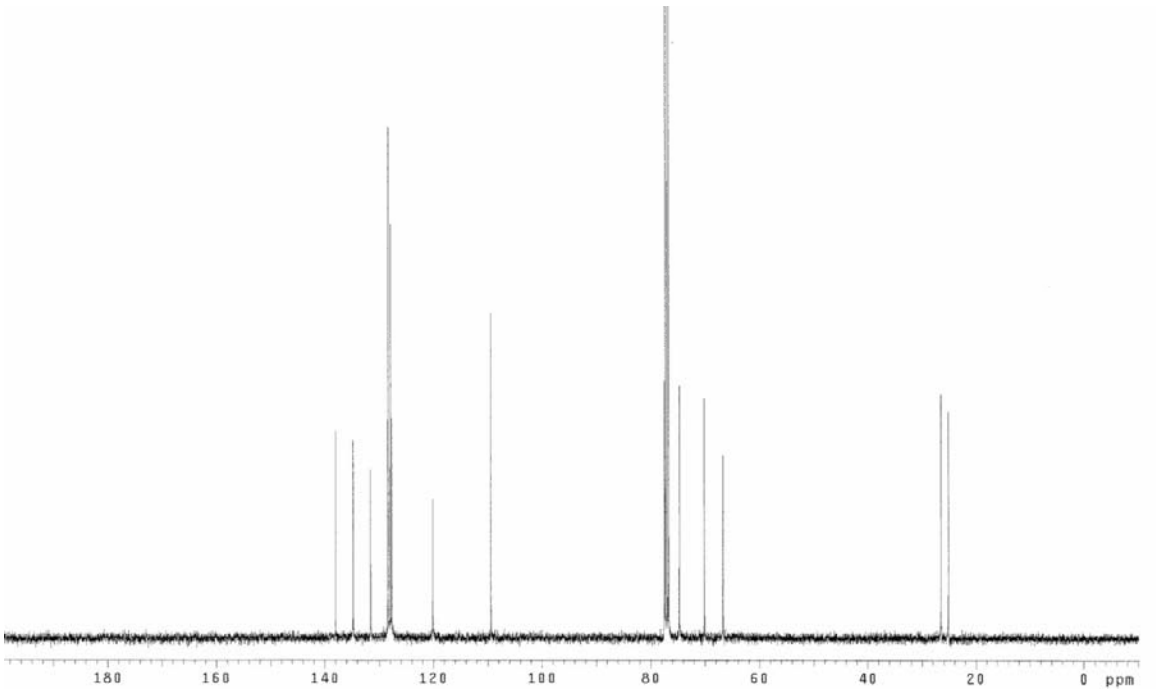

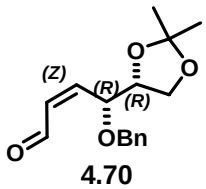
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(R)
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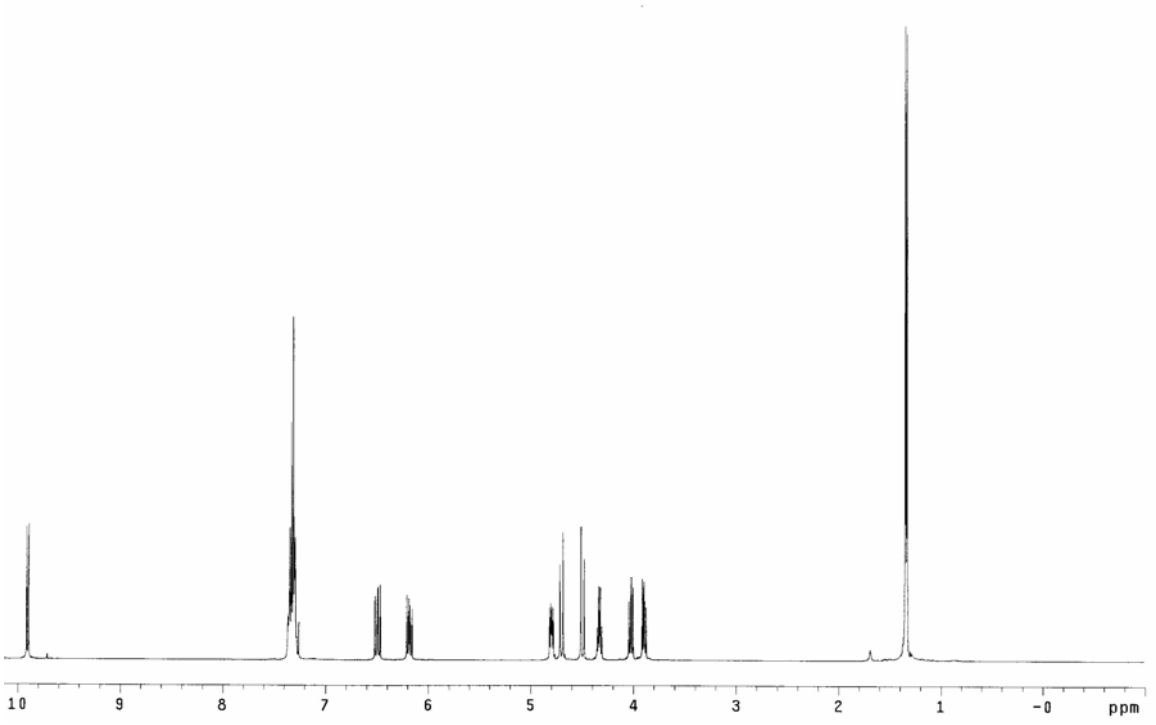
4.70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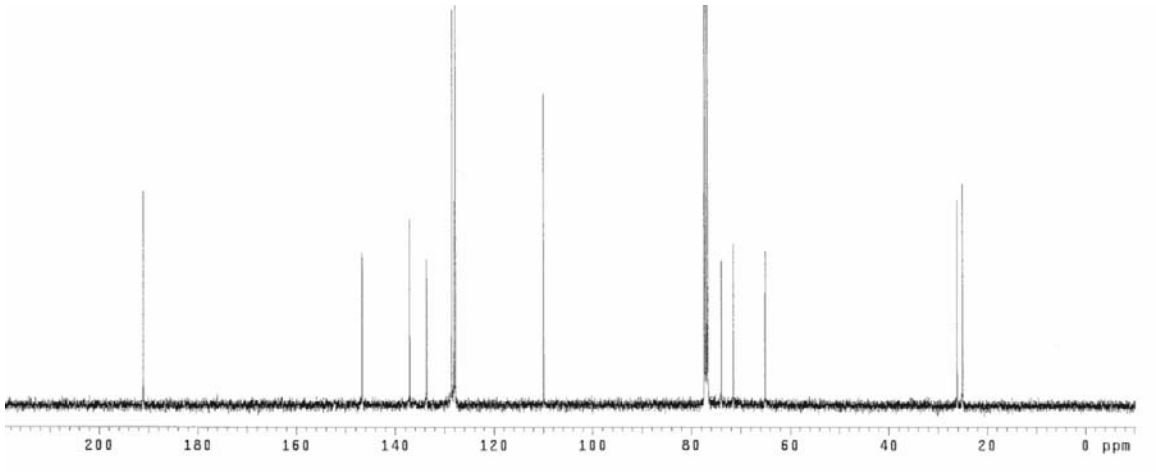
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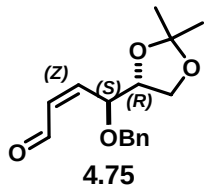
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(S)
(R)
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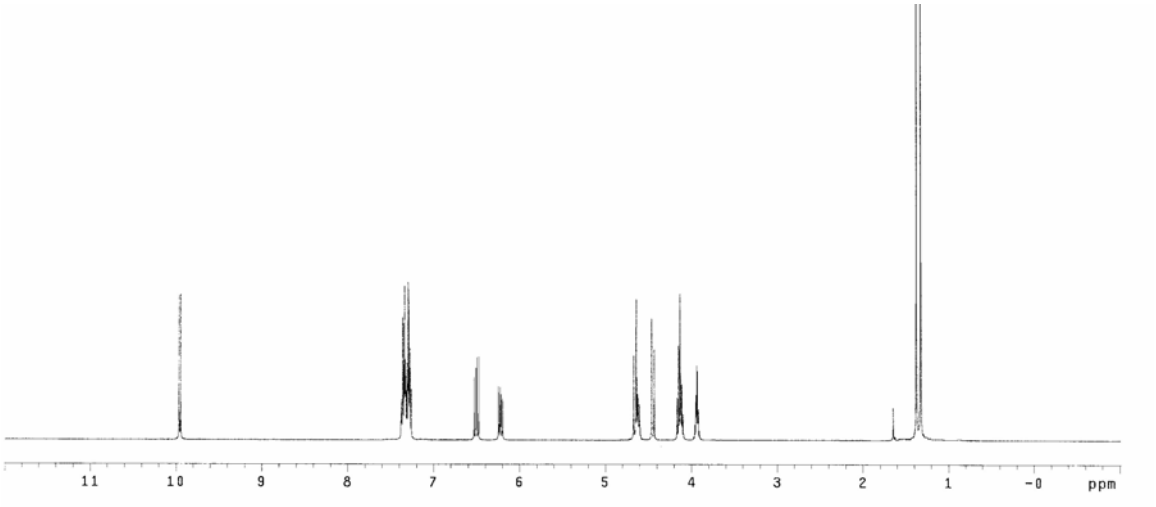
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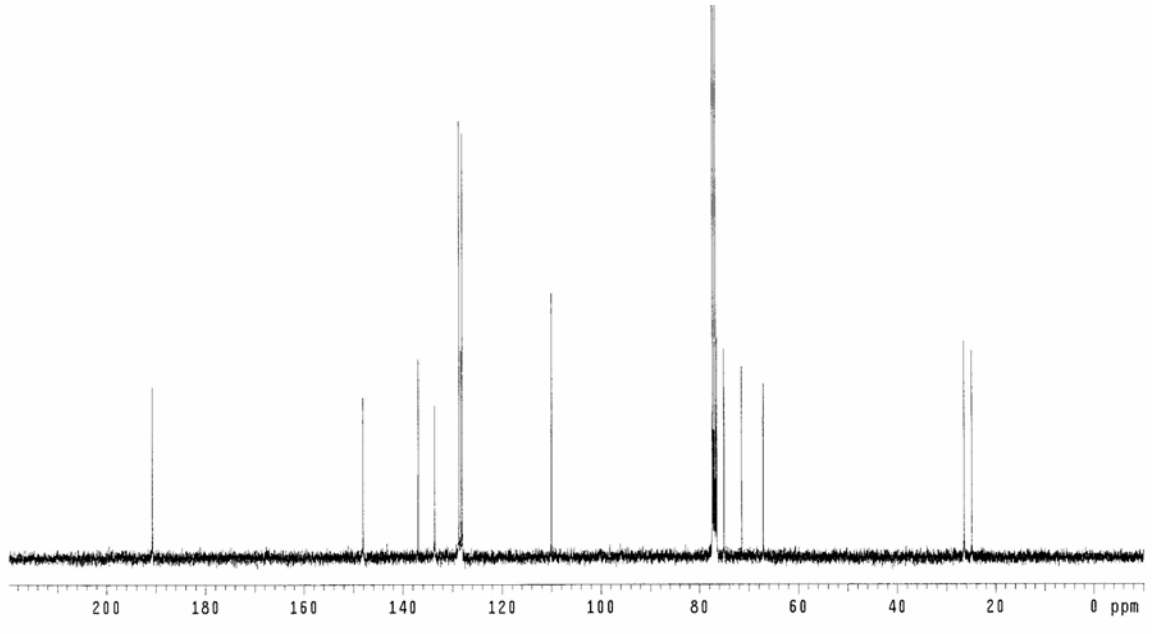
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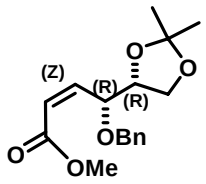
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(R)
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O
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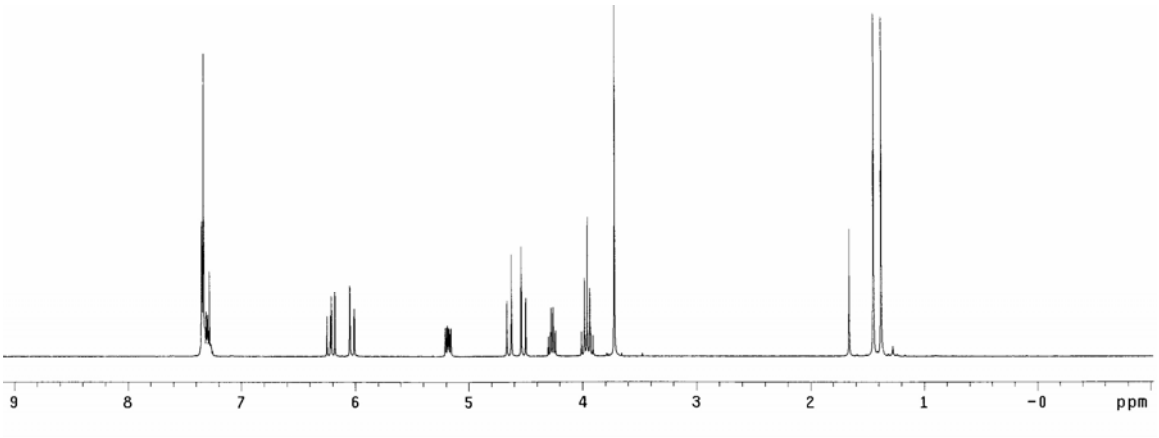
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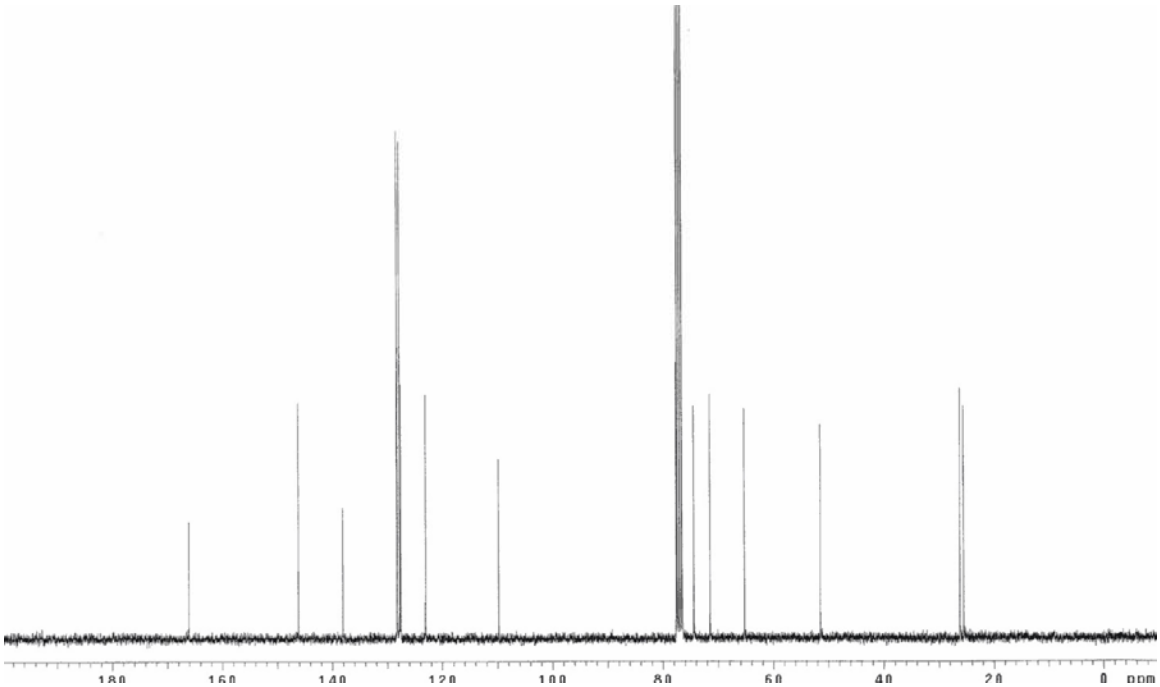
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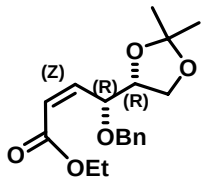
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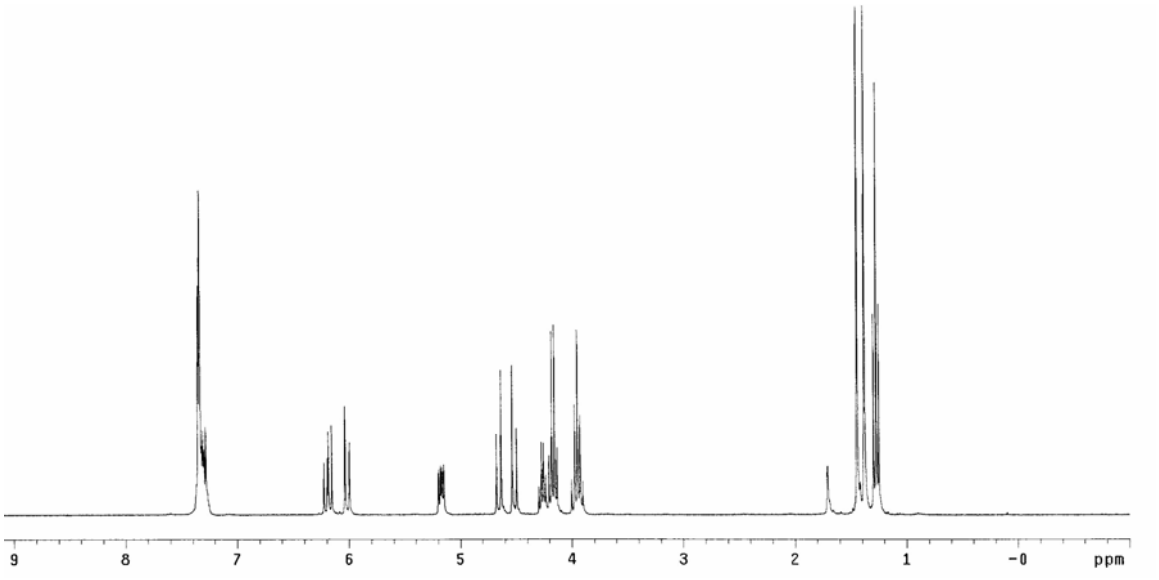
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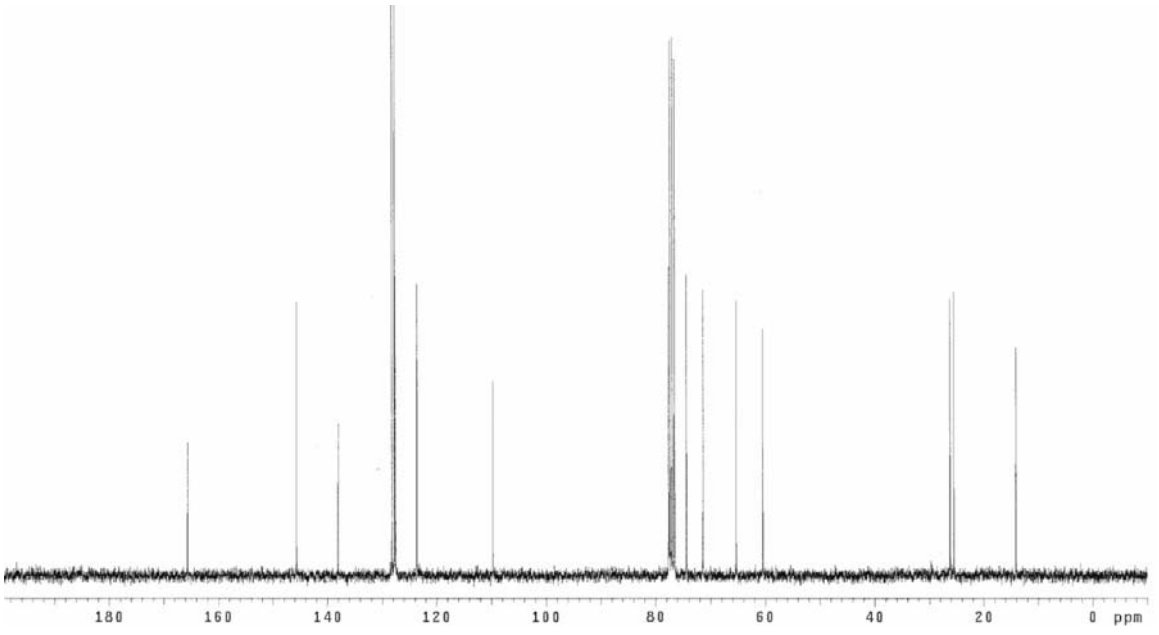
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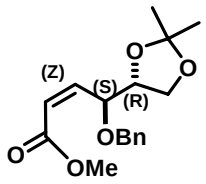
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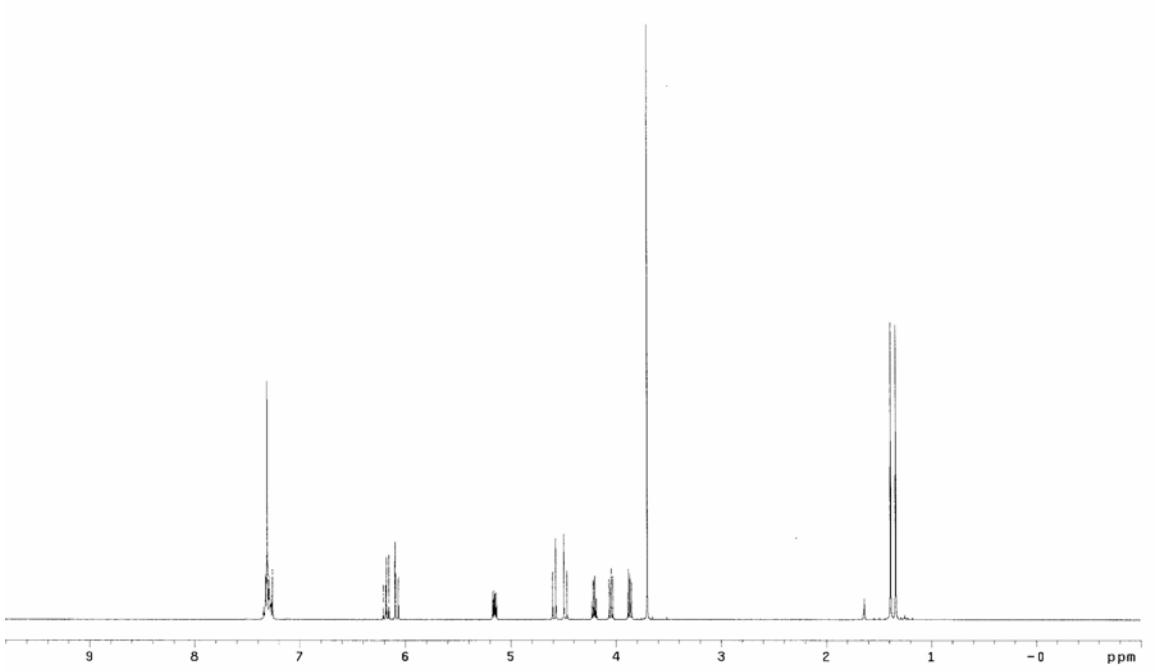
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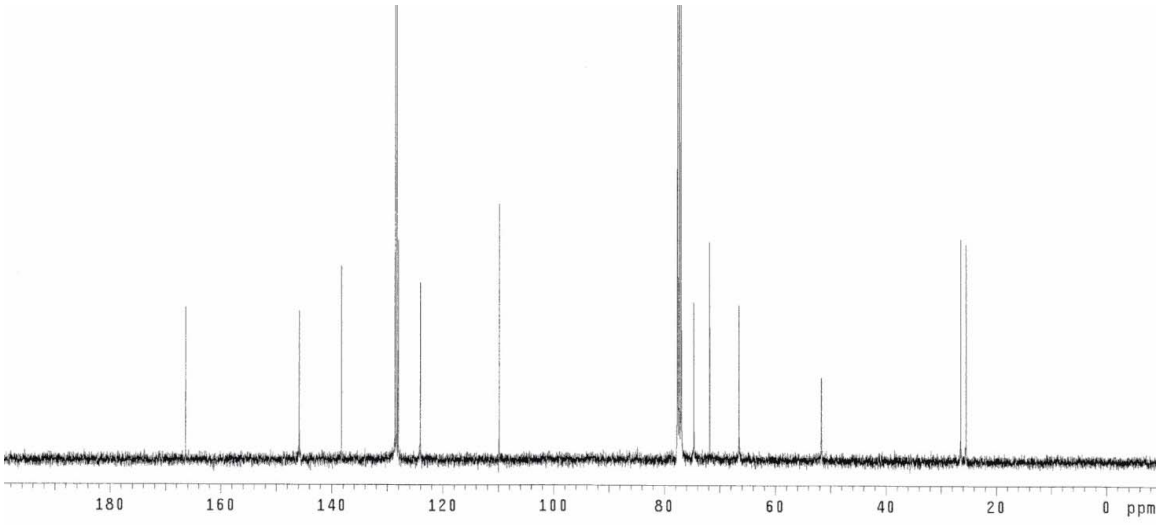
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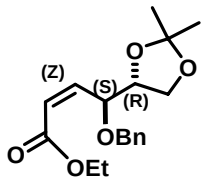
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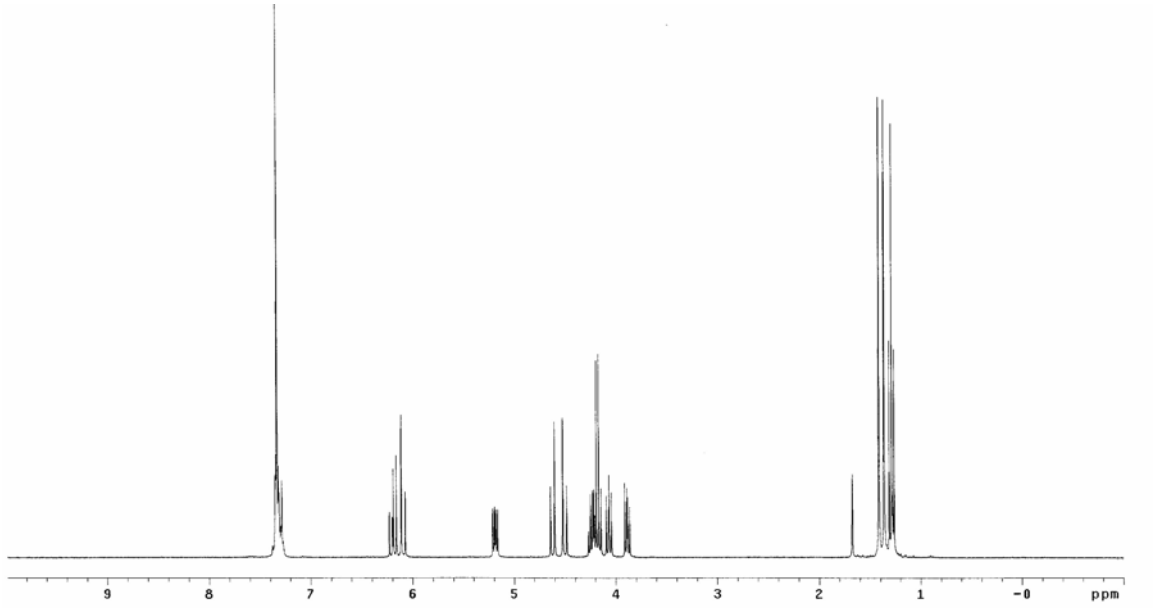
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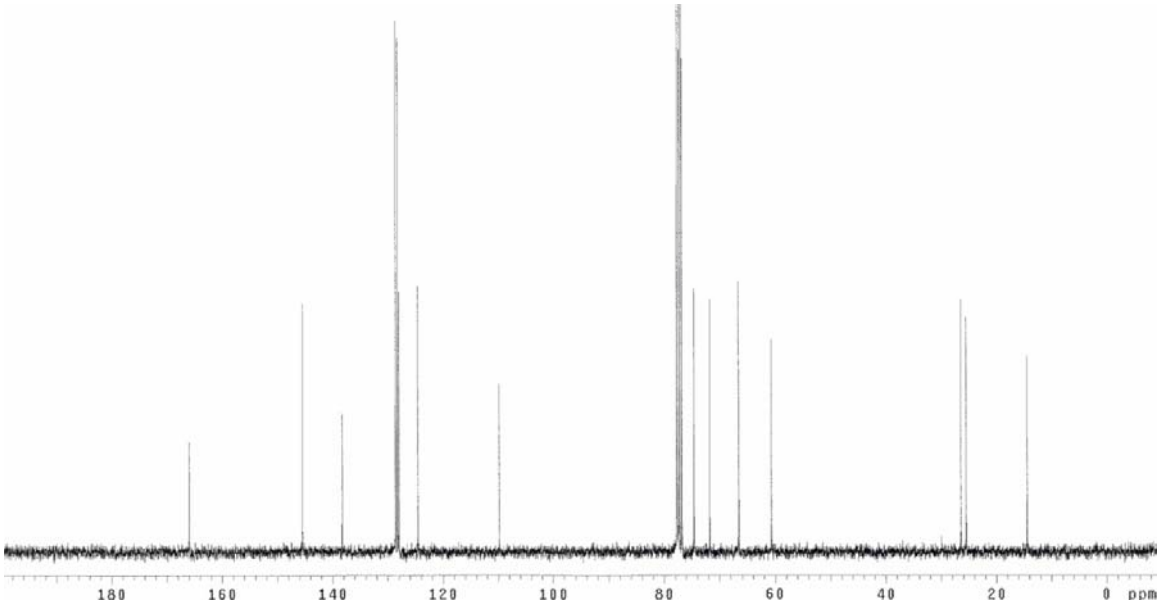
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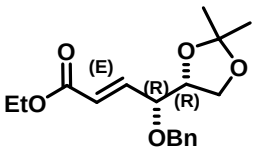
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(R)
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OBn

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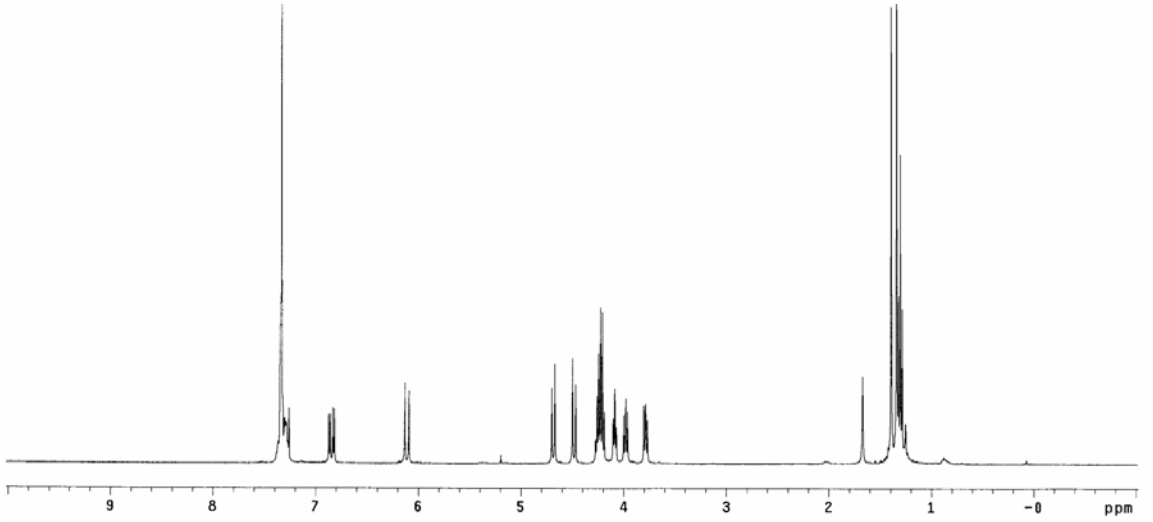
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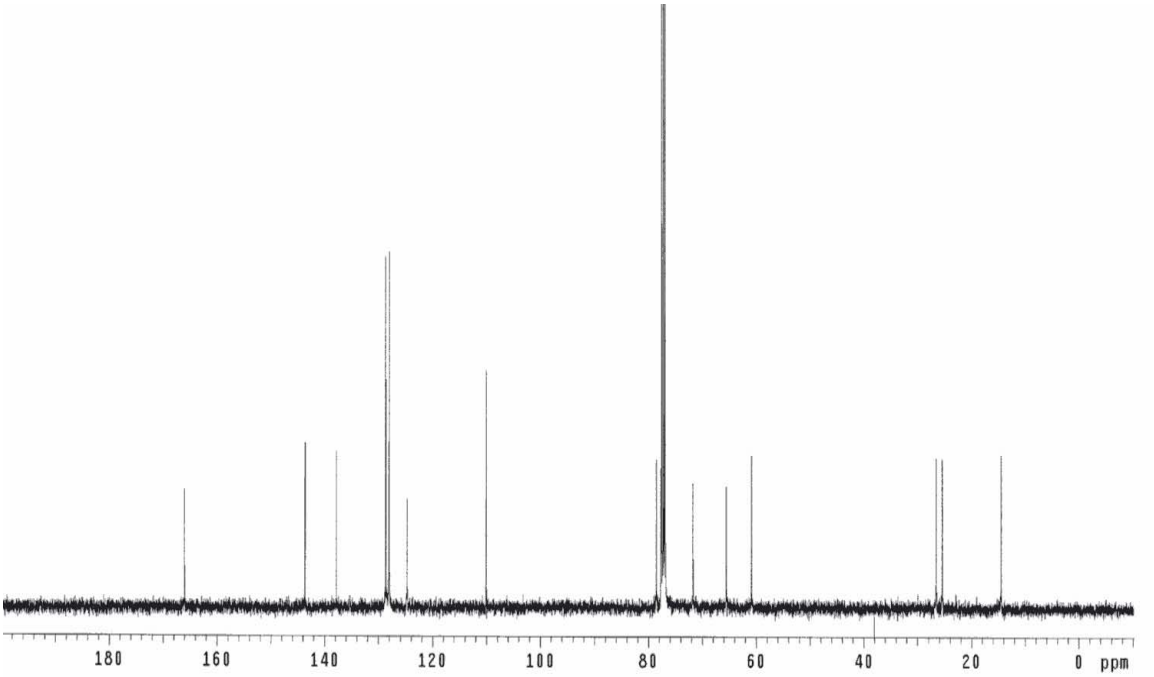
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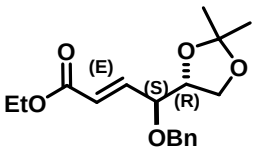
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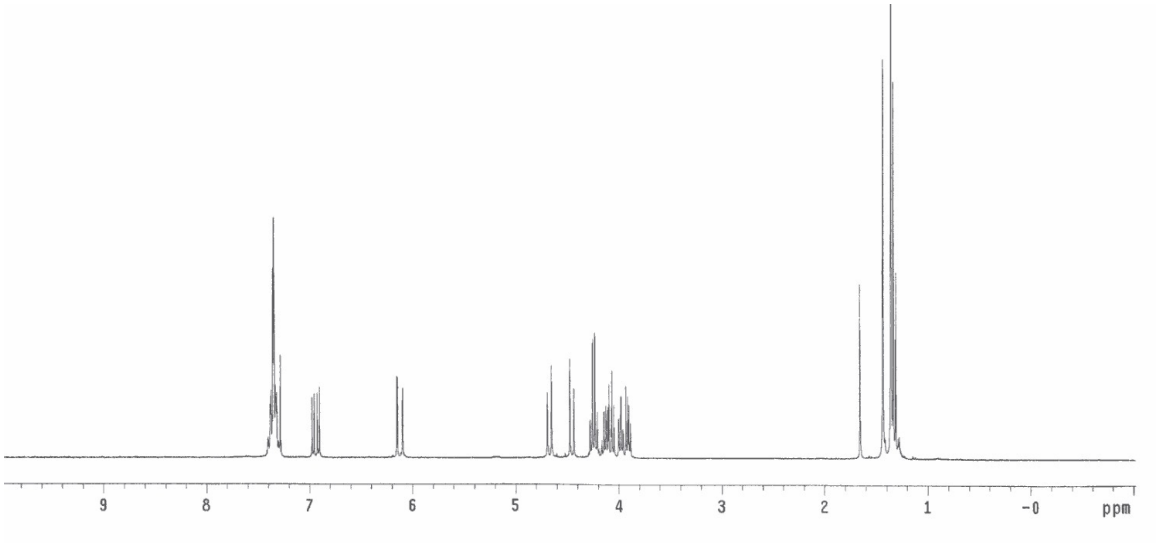
(R)
OBn

4.78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-0
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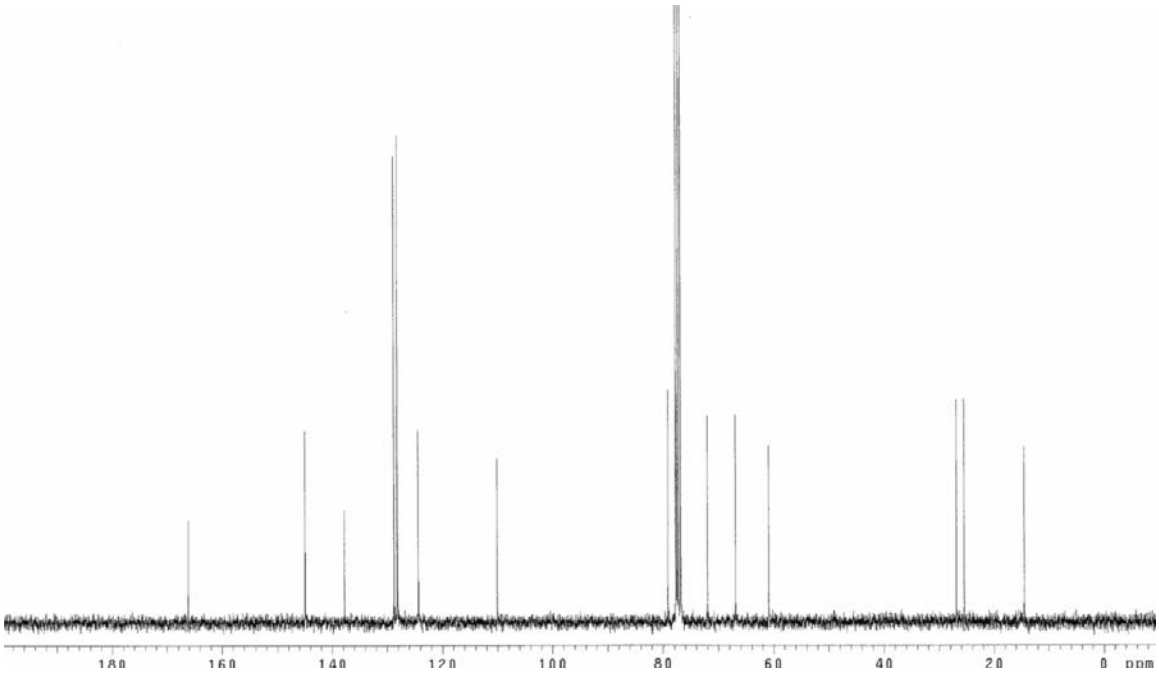
180
160
140
120
100
80
60
40
20
0
ppm

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Chapter 5 Nucleophilic Catalysis *via* Phosphine Conjugate Addition

5.1 BACKGROUND

Organophosphorous compounds have been increasingly important in organic synthesis. Generally, phosphines serve as precursors to phosphonium ylides in the Wittig reaction,[1] and as nucleophilic triggers in the Misunobu reaction.[2] In these processes, the phosphine is stoichometrically consumed and converted into a phosphine oxide. Phosphines are also commonly used as ligands in transition metal catalysis to control reactivity and selectivity.[3] Despite the long history of organophosphorous compounds as stoichiomeric reagents and ligands, the use of phosphines as nucleophilic catalysts was first introduced in 1963 by Rauhut and Currier.[4] Recently, nucleophilic phosphine catalysis has received extensive attention in organic synthesis. For example, the phosphine-catalyzed Baylis-Hillman reaction is one of the most powerful methods for C-C bond formation.[5] As nucleophilic catalysts, phosphines should have the balance of nucleophilicity, leaving group ability, and the ability to stabilize an adjacent carbanion. It is well documented that triaryl phosphines are better nucleophiles than the corresponding amines. For example, the rate of the S_N2 reaction of EtI with Et_2PhP is over 500 times faster than with Et_2PhN.[6] Indeed, triakylphosphines have even better nucleophilicity than triaryl phosphines. In general, increasing leaving group ability is correlated with decreasing basicity. The pKa values of triethylphosphosphonium ($HPEt_3^+$) and triethylammonium ($HNEt_3^+$) are 8.7 and 10.7, respectively. These pKa values indicate that triethylphosphine is a better leaving group than triethylamine. Finally, phosphines have a special ability to stabilize the carbanion generated from nucleophilic addition to conjugated carbonyl compounds *via* an electrostatic interaction between the positive charge on phosphonium and the negative charge on the enolate oxygen. The combination

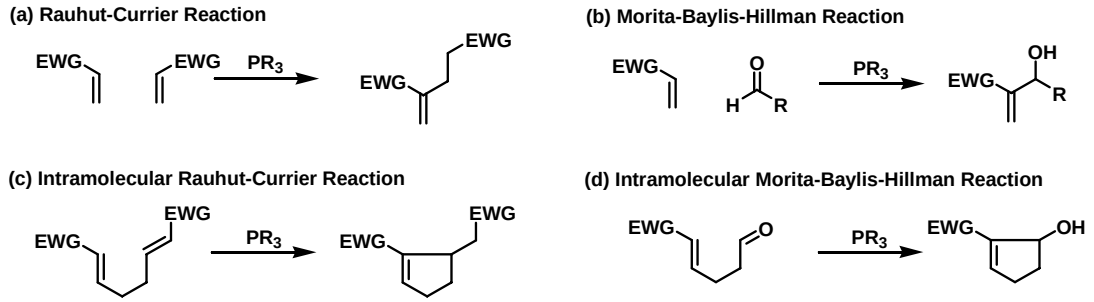
of these unique properties allow phosphines to act as both strong nucleophiles and good leaving groups, fulfilling the critical requirements for nucleophilic catalysts.

The Krische group has been very interested in the development of catalytic systems for the nucleophilic activation of enones utilizing phosphine catalysts. Recently, an intramolecular variant of the Rauhut-Currier reaction was developed in our lab.[7] To further extend nucleophilic phosphine catalysis, we have attempted to develop new catalytic transformations employing phosphines as catalysts. Here we report two new methodologies related to nucleophilic phosphine catalysis: (1) catalytic cycloallylation *via* nucleophilic phosphine catalysis and (2) allylic amination of Morita-Baylis-Hillman acetates.

5.2 CATALYTIC CYCLOALLYLATION VIA NUCLEOPHILIC PHOSPHINE CATALYSIS

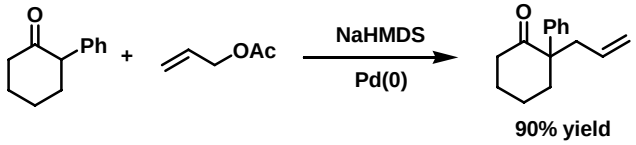
5.2.1 Introduction

Regioselective enolate generation *via* nucleophilic catalysis has been broadly utilized in organic chemistry. Additionally, the enolates generated *via* nucleophilic catalysis have been coupled to a diverse set of electrophilic partners, including carbonyl compounds and enones (Scheme 5.1).[5] The classic example of such a transformation is the organocatalytic condensation of aldehydes with α,β-unsaturated carbonyl compounds. This reaction was first described by Morita in 1968;[8] the methodology was later developed by Baylis and Hillman.[9]



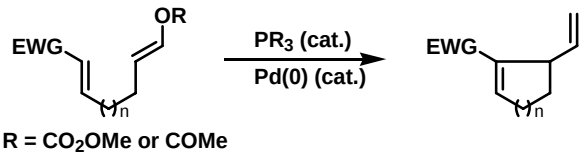
Scheme 5.1 Classic examples of nucleophilic phosphine catalysis.

In addition, it has been well documented that preformed enolates can be coupled to allylic halides[10] and "nonclassical" eletrophilic partners, such as metallo-π-allyl species.[11] Indeed, metal-catalyzed allylation of enolates has been well studied by Trost and Tsuji (Scheme 5.2).[11a,b]



Scheme 5.2 Coupling of a preformed enolate and nonclassical electrophile.

In this regard, the compatibility of palladium-based and tertiary phosphine catalytic systems suggest the feasibility of catalytic enone allylation processes, whereby activation of latent nucleophilic (enone) and electrophilic (allyl carbonate) partners is achieved through phosphine catalysis and palladium-π-allyl formation, respectively. Herein, we report catalytic enone cycloallylation *via* concomitant activation of the latent nucleophile and electrophile in an unprecedented two-component catalytic system (Scheme 5.3).[12]

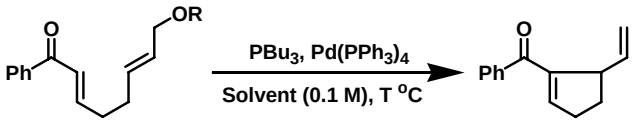


Scheme 5.3 General strategy for catalytic cycloallylation.

5.2.2 Optimization

In order to access the proposed transformation, catalytic intramolecular cycloallylation of mono-enone mono-allylic acetate **5.1** was attempted using tributylphosphine and $Pd(PPh_3)_4$ as nucleophilic and electrophilic activators, respectively. Initial experiments performed in an aprotic medium using 10 mol% $Pd(PPh_3)_4$ and 50 mol% PBu_3 resulted in a poor yield of cycloallylation product **5.3** (Table 5.1, entry 1). It was postulated that capture of the metallo π-allyl intermediate would be facilitated if the transiently generated enolate were stabilized in a polar solvent.[7] Accordingly, the use of *tert*-butyl alcohol as solvent increased the yield of **5.3** to 21 % at a reduced loading of $Pd(PPh_3)_4$ (Table 5.1, entry 2). When the loading of PBu_3 was increased to 100 mol%, the yield increased to 67 % (Table 5.1, entry 3). Gratifyingly, when mono-enone mono-allylic carbonate **5.2** was used as substrate instead of mono-enone mono-allylic acetate, the yield increased dramatically to 92 % (Table 5.1, entry 4). It was rationalized that either methoxy ion or methyl carbonate ion, generated in the palladium-π-allyl formation step, facilitated the β-elimination reaction to regenerate the phosphine catalyst, thus improving the yield. This enhanced yield was found to persist even at 1 mol% loading of $Pd(PPh_3)_4$ (Table 5.1, entry 5).

Table 5.1 Optimization table of catalytic cycloallylation.



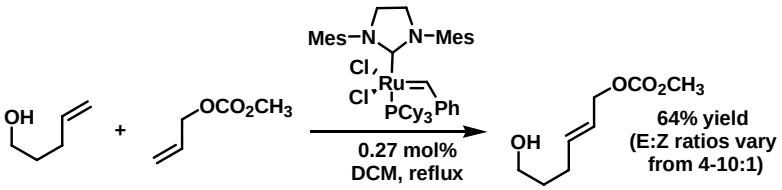
5.1, R = $COCH_3$
5.2, R = CO_2CH_3

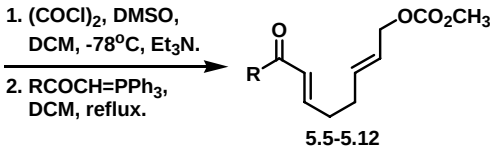
5.3

entry	R	solvent	$Pd(PPh_3)_4$ (mol%)	PBu_3 (mol%)	*T* (°C)	yield (%)
1	$COCH_3$	THF	10	50	60	6
2	$COCH_3$	*t*-BuOH	4	50	30	21
3	$COCH_3$	*t*-BuOH	4	100	60	67
4	CO_2CH_3	*t*-BuOH	5	100	60	92
5	CO_2CH_3	*t*-BuOH	1	100	60	92

5.2.3 Preparation of substrates

After optimization, a set of structurally diverse substrates was synthesized via concise synthetic pathways: (1) cross-metathesis using Grubbs-II,[13] (2) Swern oxidation,[14] and (3) Wittig reaction[1] (Scheme 5.4).





5.5-5.12

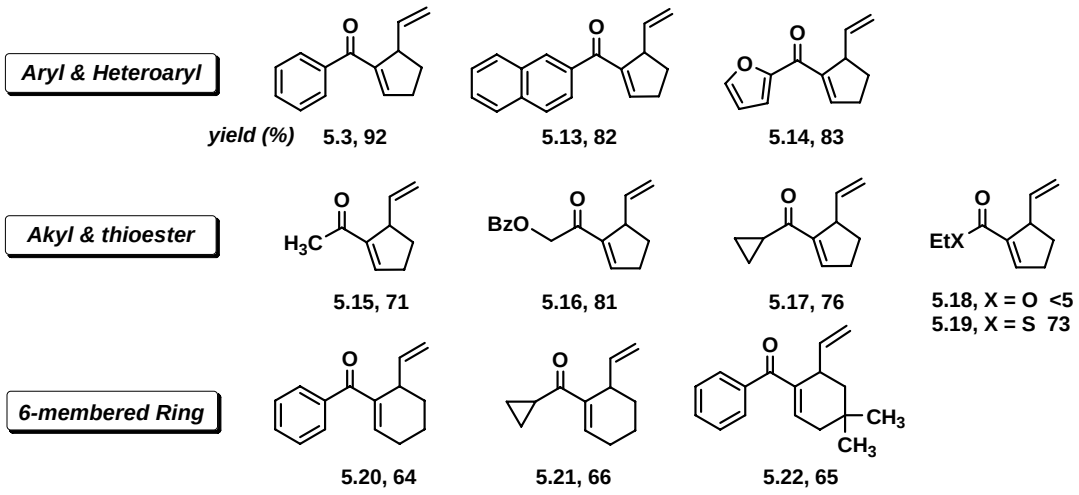
Overall Yield (step1 and 2)
5.5, R = phenyl, 75%
5.6, R = 2-naphthyl, 51%
5.7, R = 2-furyl, 52%
5.8, R = Methyl, 73%
5.9, R = benzoyloxymethyl, 82%
5.10, R = cyclopropyl, 79%
5.11, R = ethoxy, 96%
5.12, R = thoethyl, 71%

Scheme 5.4 Preparation of substrates.

5.2.4 Substrate Scope

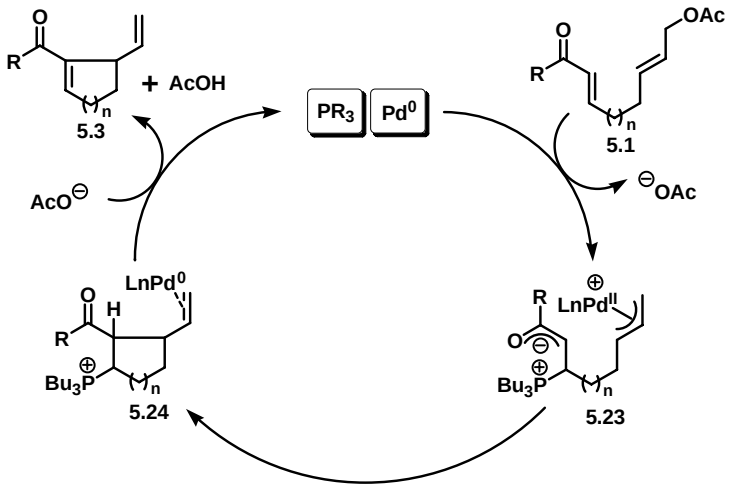
With these substrates in hand, the scope of the catalytic cycloallylation was examined. Aromatic and heteroaromatic enone substrates **5.6** and **5.7** successfully participated in the reaction to provide the corresponding products **5.13** and **5.14** in 82% and 83% yield, respectively. Aliphatic enone substrates **5.8** and **5.9** (i.e. methyl and benzoyloxymethyl substituted enone) underwent cycloallylation to produce the cycloallylation products **5.15** and **5.16** in good yields. The cycloallylation of cyclopropyl substituted enone **5.10** is noteworthy, as cyclopropanes possessing adjacent π-unsaturation are known to react readily with low-valent transition-metal complexes. However, cyclopropyl functionality was tolerated under the reaction conditions to provide the desired product **5.17** in 76% yield. Whereas enoate **5.11** provided only trace amounts of cycloallylation product **5.18**, the corresponding thioenoate **5.12** was readily cyclized to produce the desired product **5.19** in 73 % yield. This result is consistent with enhanced performance of thioenoates in Morita-Baylis-Hillman-type cyclizations[15] and is remarkable in view of the well-established susceptibility of thioesters to oxidative addition by low-valent palladium.[16] Finally, the cycloallylation reaction extends to the formation of six-membered rings. Aromatic and aliphatic substituted enones provided six-membered cycloallyation products 5.**20**-**5.22** in good yields. On the basis of the Thorpe-Ingold effect,[17] it was assumed that conformationally predisposed substrates possessing geminal substitution would provide better yields. However, it turned out the Thorpe-Ingold effect was not applicable to this catalytic system since cycloallytion products **5.20** and **5.22** were obtained in almost the same yield (Table 5.2)

Table 5.2 Catalytic cycloallylation of mono-enone mono-allylic carbonate.



5.2.5 Mechanistic Studies

Based on our experimental data, a plausible catalytic mechanism was proposed. Our proposed mechanism arises from the combination of the nucleophilic features of the Morita-Baylis-Hillman reaction with the electrophilic features of the Trost-Tsuji reaction. The proposed catalytic cycle begins with the nucleophilic 1,4-addition of tributyl-phosphine to mono-enone mono allylic acetate **5.1** to reversibly generate a zwitterionic enolate. This addition is accompanied by palladium-π-allyl formation to generate complex **5.23**, which undergoes enolate alkylation to yield intermediate **5.24**. Finally, β-elimination assisted by acetate ion provides cycloallylation product **5.3** and regenerates phosphine and palladium catalysts (Scheme 5.5).

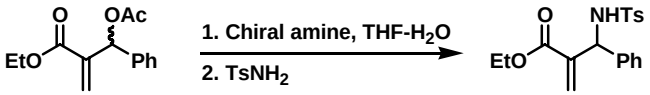


Scheme 5.5 Plausible catalytic cycle.

5.3 REGIOSELECTIVE ALLIC AMINATION OF MORITA-BAYLIS-HILLMAN ACETATES

5.3.1 Introduction

The synthesis of β-amino acids[18] has been of considerable interest, not only because they are useful precursors of β-peptides[19] and β-lactams,[19b,20] but also many β-amino acids show antibiotic, antifungal, cytotoxic or other important biological properties in their free form or as part of peptidic products.[21] The Morita-Baylis-Hillman (MBH) reaction with imine electrophiles has been utilized in the synthesis of β-amino acids. Recently, an alternative method exploring a two-step protocol for the amination of Morita-Baylis-Hillman acetates using stoichiometric DABCO was reported by Kim.[22] In 2002, Kim also reported the catalytic asymmetric allylic amination of Morita-Baylis-Hillman acetates using cinchonidines, such as $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ (Scheme 5.6).[23]



entry	Chiral amine (mol%)	yield (%)	% ee
1	$(DHQD)_2PHAL$ (10 mol%)	9	44
2	$(DHQD)_2PHAL$ (50 mol%)	12	70

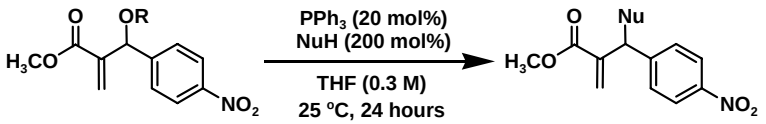
Scheme 5.6 Kim's asymmetric allylic amination using chiral amine.

However, Kim's protocol suffers from unsatisfactory chemical yields, and limited scope since only aryl substituted substrates participate. In order to overcome the limitations with tertiary amine-based regioselective allylic amination of Morita-Baylis-Hillman acetates, we have attempted to apply nucleophilic phosphine catalysis to allylic amination reaction. Herein, we report the phosphine catalyzed regioselective allylic amination of Morita-Baylis-Hillman acetates.[24]

5.3.2 Optimization

In order to investigate the leaving group effect, compounds **5.25-5.28** were prepared and subjected to regioselective allylic amination. From this investigation, we found that the ΔpK_a between the conjugate acid of the leaving group and the pronucleophile played a very important role in the allylic amination reaction. If the pK_a of the conjugate acid of the leaving group is too low, the deprotonation of the pronucleophile is inefficient (Table 5.3, entries 1 and 2). Finally, slightly lower pK_a of the conjugate acid of the leaving group and 4,5-dichlorophthalimide pronucleophile gave the optimum yield (Table 5.3, entry 6).

Table 5.3 Optimization table of regioselecitve allylic amination.



entry	Substrate		NuH	Yield (%)
1	R = $PO(OEt)_2$	12	4,5-Dichlorophthalimide	3
2	R = *p*-NO_2Bz	13	4,5-Dichlorophthalimide	32
3	R = BOC	14	Phthalimide	12
4	R = BOC	14	4,5-Dichlorophthalimide	77
5	R = Ac	15	Phthalimide	8
6	R = Ac	15	4,5-Dichlorophthalimide	90

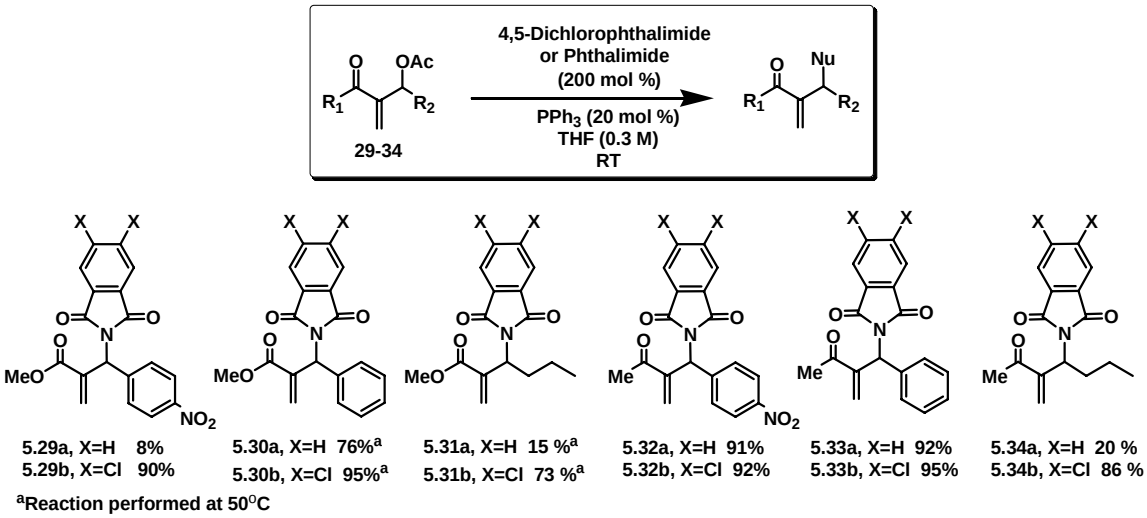
5.3.3 Substrate Scope

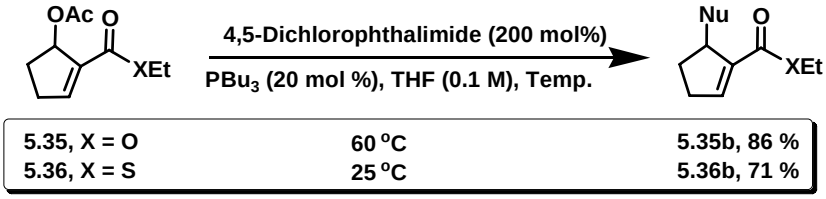
Under the optimized reaction conditions, the scope of the catalytic allylic amination was examined with a set of structurally diverse substrates. In the case of enoate substrates **29-31**, 4,5-dichlorophthalimide gave better yields than phthalimide due to the difference of pK_a values between the conjugate acids of the leaving group and pronucleophile. However, in case of the enone substrates, the aryl substituted substrates **32** and **33** were less sensitive to the pronucleophile due to the enhanced substrate electrophilicity. Interestingly, the alkyl substituted substrate **34** was sensitive to the pronucleophile, presumably resulting from the lower electrophilicity of alkyl substituted enone substrate compared to aryl substituted enones (Table 5.4).

One of the great advantages of phosphine catalyzed allylic amination of Morita-Baylis-Hillman acetates is the extension to β-substituted substrates. These substrates are not compatible with DABCO catalyst.[22] For β-substituted α,β-unsaturated carbonyl compounds, a more nucleophilic phosphine than triphenylphosphine is required, and trialkylphosphines were investigated.[15] Upon exposure of the β-substituted substrates

5.35 and **5.36** to tributylphosphine catalyzed allylic amination reaction, we observed efficient conversion to give amination products **5.35b** and **5.36b** in good yield (Scheme 5.7).

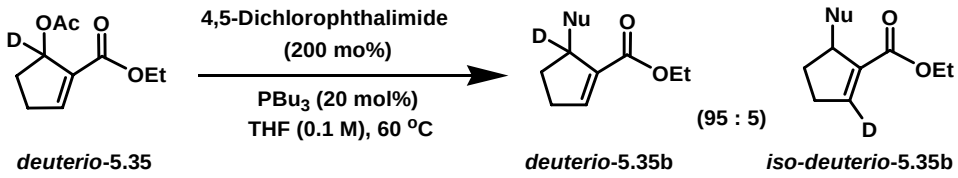
Table 5.4 Regioselective allylic amination of MBH acetates.





Scheme 5.7 Regioretentive allylic amination of cyclic MBH acetates.

For substrates **5.35** and **5.36**, the catalyzed and uncatalyzed imide addition would afford identical products. In order to identify the operative reaction manifold, *deuterio*-**5.35** was prepared and subjected to the optimized reaction conditions. Substitution was found to occur with 95:5 retention of regiochemistry, strongly supporting a reaction proceeding through a phosphine catalyzed tandem S_N2'-S_N2' pathway (Scheme 5.8).



Scheme 5.8 Deuterium labeling study.

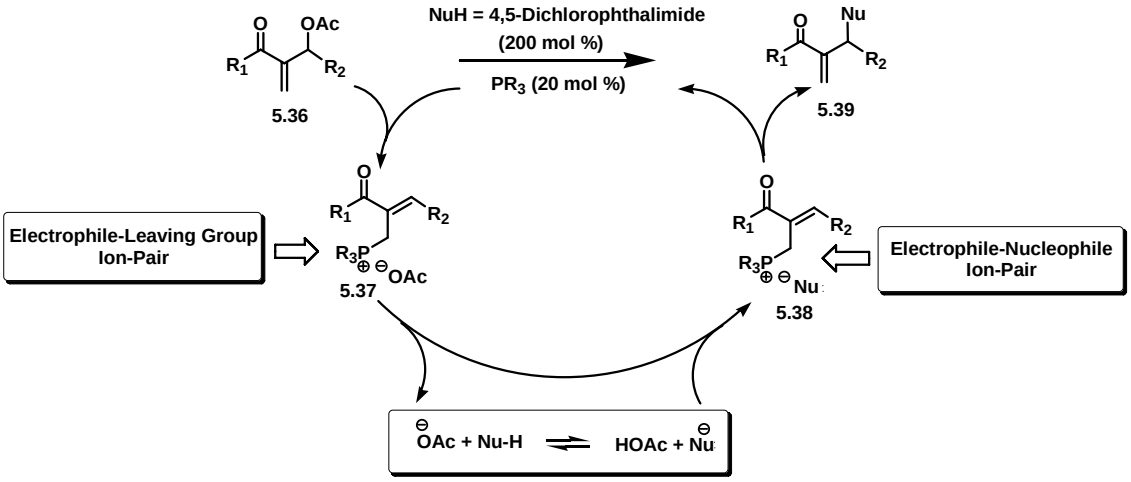
5.3.4 Mechanistic Studies

Based on deuterium labeling studies and experimental data, a plausible catalytic mechanism was proposed. It is suggested that the allylic amination of Morita-Baylis-Hillman acetates occurs through a successive S_N2'-S_N2' mechanism. A nucleophilic tertiary phosphine undergoes 1,4-addition to the allylic substrate **5.36** followed by elimination of acetate anion via S_N2' type reaction to generate a quaternary phosphonium salt, which is stabilized by acetate anion to give an electrophile-leaving group ion-paired species **5.37**. Acetate anion then activates the pronucleophile *via* acid-base reaction to generate an anionic nucleophile, followed by the formation of electrophile-nucleophile ion-pair to give intermediate **5.38**. Finally, the anionic nucleophile undergoes a second S_N2' reaction to provide the allylic amination product **5.39** and regenerate the phosphine catalyst (Scheme 5.9).

5.3.5 Deracemization of Morita-Baylis-Hillman Acetates

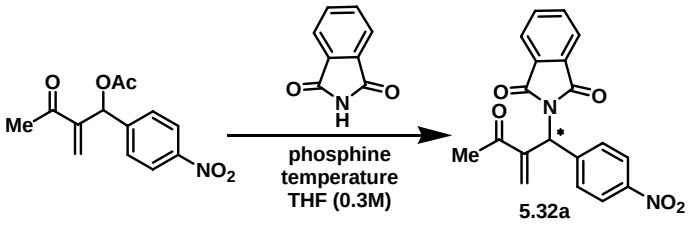
To investigate the feasibility of Morita-Baylis-Hillman acetates deracemization, commercially available chiral phosphines were screened. As a result, (*R*)-Cl-MeO-

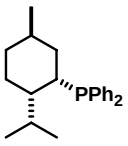
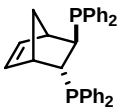
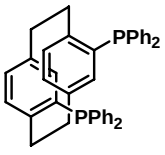
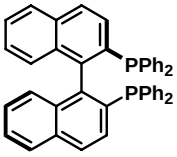
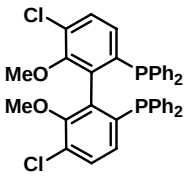
BIPHEP under optimized conditions provided amination product **5.32a** in 80 % yield as a 78:22 ratio of enantiomers (Table 5.5).



Scheme 5.9 Proposed catalytic cycle.

Table 5.5 Establishing the feasibility of deracemization.



(S)-NMDPP	(R,R)-NORPHOS	(S)-PHANEPHOS	(R)-BINAP	(R)-Cl-MeO-BIPHEP
				
25 °C	25 °C	25 °C	25 °C	50 °C
44H	12H	48H	48H	66H
85.6 % yield	90.2 % yield	74.8 % yield	80 % yield	80 % yield
29.3% ee (MeOH)	27.7% ee (iPrOH)	39.1% ee (iPrOH)	3% ee (iPrOH)	56% ee (MeOH)

5.4 SUMMARY AND CONCLUDING REMARKS

We have shown that catalytic enone cycloallylation occurs *via* concomitant activation of latent nucleophilic and electrophilic partners. This cycloallylation is achieved through the use of a two-component catalyst system uniting the nucleophilic features of the Moria-Baylis-Hillman reaction with the electrophilic features of the Trost-Tsuji reaction. In addition, we have demonstrated the first phosphine-catalyzed intermolecular allylic amination of Morita-Baylis-Hillman acetates. Furthermore, this methodology was extended to β-substituted systems which *N*-nucleophilic system (e.g. DABCO) cannot catalyze. Additionally, a deuterium labeling study strongly supports our proposed mechanism. Though a deracemization reaction did not provide a high ee, it suggests that deracemization is feasible with further optimization. Finally, the regioselective allylic amination of MBH acetates provides strong support for the possibility of allylic alkylation of Morita-Baylis-Hillman acetates.

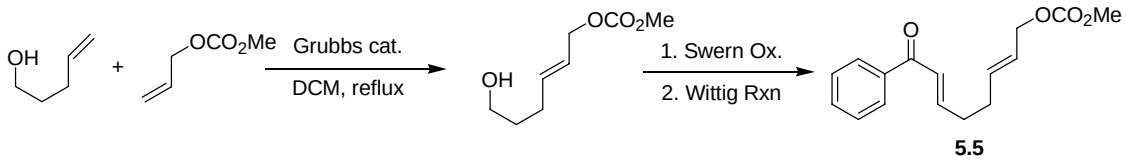
5.5 EXPERIMENTAL SECTION

5.5.1 General

All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. Dichloromethane (DCM) was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. Solvents for chromatography are listed as volume/volume ratios. Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M + 1) or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian Gemini (400 MHz or 300MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (pip) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. Enantiomeric purity was determined using a Varian Pro Star HPLC equipped with Chiralcel OD column, eluting with 15% isopropanol in hexane.

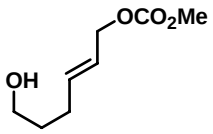
5.5.2 Catalytic Enone Cycloallylation

Representative Procedure for Synthesis of mono-enone mono-allylic carbonate.



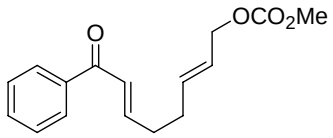
5.5

To a degassed solution of bis(tricyclohexylphosphine)benzylidine ruthenium (IV) dichloride (Grubbs second-generation catalyst) (250 mg, 0.29 mmol, 0.27 mol%) in CH_2Cl_2 (460 mL) was added 4-penten-1-ol (10 g, 116 mmol, 110 mol%) and allyl methyl carbonate (12g, 106 mmol, 100 mol%). The reaction was allowed to stir at reflux for 12 hours. The solvent was evaporated *in vacuo* and the reaction was purified *via* flash chromatography (7:3 Haxane:EtOAc) to provide the allylic carbonate (11.6 g, 64 %) as a yellow oil, with an alkene isomer ratio of 6:1. This ratio varied from 4:1-10:1. Spectral data for the major isomer is reported.



Carbonic acid 6-hydroxy-hex-2-enyl ester methyl ester. ^{1}H NMR (400 MHz, $CDCl_3$): 5.75 (dt, J = 15.4, 6.7 Hz, 1H), 5.54 (dtt, J = 15.4, 6.5, 1.5 Hz, 1H), 4.49 (dd, J = 1.0, 6.5 Hz, 2H), 3.69 (s, 3H), 3.52 (q, J = 5.9 Hz, 2H), 2.51 (t, J = 5.0 Hz, 1H), 2.07 (q, J = 7.2 Hz, 2H), 1.57 (dt, J = 14.7, 6.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.5, 136.3, 123.5, 68.3, 61.7, 54.5, 31.4, 28.3. HRMS Calcd. for $C_8H_{14}O_4$ (M+1): 175.0970, Found: 175.0974. FTIR (neat): 3375, 2941, 1747, 1445, 1259, 942, 793 cm^{-1}.

A stirred solution of oxalyl chloride (1.4 mL, 13.8 mmol, 120 mol%) in CH_2Cl_2 (50 mL, 0.28 M) was cooled to -78 ^oC in a dry ice-acetone bath. To this solution was added a solution of DMSO (2.0 mL, 27.6 mmol, 240 mol%) in CH_2Cl_2 (25 mL) at -78 ^oC. The reaction was allowed to stir for 15 minutes. To the reaction was added a solution of the allylic carbonate (2.0 g, 11.5 mmol, 100 mol%) in CH_2Cl_2 (25 mL) at -78 ^oC. The final reaction concentration was 0.11 M with respect to allylic carbonate. The reaction was allowed to stir for 45 minutes in -78 ^oC. Neat triethylamine (8 ml, 58 mmol, 500 mol%) was added and the reaction was allowed to stir at -78 ^oC for 10 minutes, followed by warming to room temperature. The reaction mixture was washed with ammonium chloride, water, and brine successively and then dried over sodium sulfate and concentrated *in vacuo*. $CHCl_3$ (100 mL, 0.1 M in **1a'**) and 1-phenyl-2-(triphenyl)-λ^5-phosphanylidene)-ethanone (8.7g, 23.0 mmol, 200 mol%) was added. The reaction was heated to reflux and allowed to stir for 12 hours. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography (7:3 Hexane:EtOAc) to afford 2.4 g (75 % over two steps) of **5.5** as colorless oil. This substrate was isolated as a 4:1 mixture of alkene isomers at the position of the allylic carbonate.

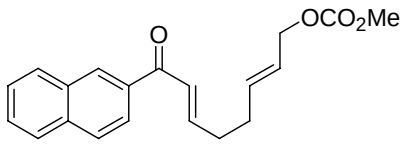


5.5

This substrate was isolated as a 4:1 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

Carbonic acid methyl ester 8-oxo-8-phenyl-octa-2,6-dienyl ester (**5.5**). ^1H NMR (400 MHz, $CDCl_3$): 7.91 (dd, J = 8.2, 1.0 Hz, 2H), 7.54 (td, J = 7.4, 1.4 Hz, 1H), 7.46 (t, J =

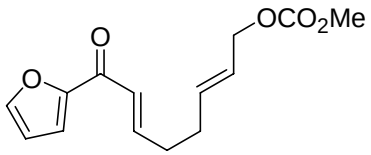
7.7 Hz, 2H), 7.01 (dt, *J* = 15.4, 6.8 Hz, 1H), 6.88 (d, *J* = 15.4 Hz, 1H), 5.83 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.66 (dt, *J* = 14.4, 6.3 Hz, 1H), 4.57 (d, *J* = 6.5 Hz, 2 H), 3.75 (s, 3H), 2.42 (dt, *J* = 7.9, 6.7 Hz, 2H), 2.30 (dt, *J* = 7.2, 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 190.9, 155.8, 148.5, 138.1, 135.4, 132.9, 128.8, 126.7, 124.8, 68.5, 63.6, 55.0, 32.6, 32.2, 30.9, 26.4. HRMS Calcd. for $C_{16}H_{18}O_4$ (M+1): 275.1283, Found: 275.1271. FTIR (neat): 3028, 2947, 1751, 1671, 1621, 1447, 1267, 974, 944 cm^{-1}.



5.6

This substrate was isolated as a 4:1 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

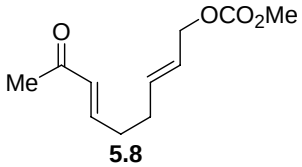
Carbonic acid methyl ester 8-naphthalen-2-yl-8-oxo-octa-2,6-dienyl ester (5.6). ^{1}H NMR (400 MHz, $CDCl_3$): 8.43 (s, 1H), 8.04-7.96 (m, 2H), 7.93-7.86 (m, 2H), 7.58 (dtd, *J* = 19.3, 7.4, 1.4 Hz, 2H), 7.07 (d, *J* = 4.5 Hz, 2H), 5.85 (dtt, *J* = 15.4, 6.5, 1.0 Hz, 1H), 5.70 (dtt, *J* = 15.4, 6.3, 1.4 Hz, 1H), 4.60 (dd, *J* = 6.2, 1.0 Hz, 2.0H), 3.76 (s, 3H), 2.47 (dtd, *J* = 7.2, 5.6, 1.7, 2H), 2.34 (dtd, *J* = 7.2, 5.6, 1.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 190.3, 155.5, 148.4, 135.3, 135.1, 135.0, 132.4, 129.9, 129.4, 128.4, 128.2, 127.7, 126.6, 126.3, 124.45, 124.38, 68.1, 54.6, 31.9, 30.7. HRMS Calcd. for $C_{20}H_{20}O_4$ (M+1): 325.1440, Found: 325.1444. FTIR (neat): 3061, 2952, 1747, 1667, 1618, 1442 cm^{-1}.



5.7

This substrate was isolated as a 4:1 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

Carbonic acid 8-furan-2-yl-8-oxo-octa-2,6-dienyl ester methyl ester (5.7). ^{1}H NMR (300 MHz, $CDCl_3$): 7.62 (dd, *J* = 1.4, 0.6 Hz, 1H), 7.24 (dd, *J* = 3.5, 0.8 Hz, 1H), 7.12 (dt, *J* = 15.4, 6.7 Hz, 1H), 6.81 (dt, *J* = 15.4, 1.5 Hz, 1H), 6.56 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.83 (dtt, *J* = 15.7, 6.2, 1.0 Hz, 1H), 5.66 (dtt, *J* = 15.6, 6.2, 1.1 Hz, 1H), 4.58 (dd, *J* = 5.9, 1.1 Hz, 2H), 3.78 (s, 3H), 2.40 (dtd, *J* = 14.3, 7.2, 1.4 Hz, 2H), 2.31 (dtd, *J* = 13.7, 7.0, 1.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.2, 155.8, 153.5, 147.7, 146.8, 135.4, 125.6, 124.8, 117.8, 112.6, 68.5, 55.0, 32.1, 30.9. HRMS Calcd. for $C_{14}H_{16}O_5$ (M+1): 265.1076, Found: 265.1073. FTIR (neat):3024, 2955, 1651, 1597, 1578, 1383, 1351 cm^{-1}.

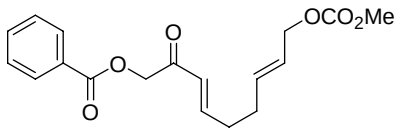


5.8

This substrate was isolated as a 61 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

Carbonic acid methyl ester 8-oxo-nona-2,6-dienyl ester (5.8). 1H NMR (300 MHz, $CDCl_3$): 6.68-6.59 (m, 1H), 5.96-5.90 (td, *J* = 1.35, 16.2 Hz, 1H), 5.54-5.47 (m, 1H), 4.43 (dd, *J* = 0.9, 6.3 Hz, 2H), 3.63 (s, 3H), 2.21-2.10 (m, 4H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 198.5, 155.7, 147.0, 135.1, 131.9, 124.8, 68.3, 54.8, 31.7, 30.7, 27.0.

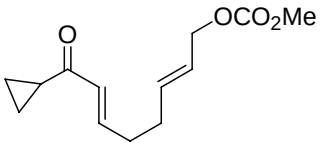
HRMS: Calcd. for $C_{11}H_{16}O_4$(M+1): 213.1127, Found: 213.1125. FTIR (neat)**:** 2957, 2254, 1748, 1696, 1674, 1443 cm^{-1}.



5.9

This substrate was isolated in >95% alkene isomeric purity.

Benzoic acid 9-methoxycarbonyloxy-2-oxo-nona-3,7-dienyl ester (**5.9**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.08 (dd, *J* = 7.9, 1.4 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 6.94 (td, *J* = 16.1, 6.8 Hz, 1H), 6.22 (d, *J* = 16.1 Hz, 1H), 5.76 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.61 (dt, *J* = 15.4, 6.3 Hz, 1H), 5.03 (s, 2H), 4.54 (dd, *J* = 6.5, 0.7 Hz, 2H), 3.74 (s, 3H), 2.33 (dt, *J* = 7.9, 6.7 Hz, 2H), 2.22 (dt, *J* = 7.5, 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 192.1, 155.4, 147.7, 134.6, 133.2, 129.7, 129.2, 128.3, 126.2, 124.6, 68.0, 67.3, 54.6, 31.7, 30.3. HRMS Calcd. for $C_{18}H_{20}O_6$ (M+1): 333.1338, Found: 333.1340. FTIR (neat): 3008, 2955, 1747, 1634, 1451, 1264, 1114, 943, 714 cm^{-1}.

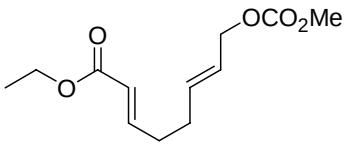


5.10

This substrate was isolated as a 10:1 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

Carbonic acid 8-cyclopropyl-8-oxo-octa-2,6-dienyl ester methyl ester (**5.10**). ^{1}H NMR (300 MHz, $CDCl_3$): 6.85-6.77 (m, 1H), 6.18 (td, *J* = 1.43, 15.6 Hz, 1H), 5.81-5.74 (m, 1H), 5.63-5.58 (m, 1H), 4.54 (dd, *J* = 0.75, 6.15 Hz, 2H), 3.74 (s, 3H), 2.32-2.21 (m, 4H),

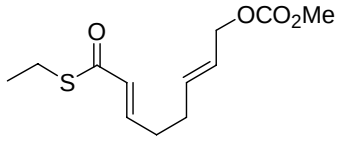
2.10-2.05 (m, 1H), 1.10-1.01 (m, 2H), 0.89-0.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 200.0, 155.5, 145.2, 135.1, 130.8, 124.4, 68.2, 54.7, 31.5, 30.6, 18.7, 11.0. HRMS: Calcd. for $C_{13}H_{18}O_4$ (M+1): 239.1283, Found: 239.1275. FTIR (neat): 3009, 2956, 1749, 1683, 1663, 1626, 1443 cm^{-1}.



5.11

This substrate was isolated in >95% alkene isomeric purity.

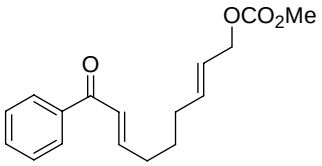
8-Methoxycarbonyloxy-octa-2,6-dienoic acid ethyl ester (**5.11**). ^{1}H NMR (300 MHz, $CDCl_3$): 6.88 (dt, *J* = 15.6, 6.5 Hz, 1H), 5.81-5.71 (m, 2H), 5.59 (dtt, *J* = 15.6, 6.2, 1.3 Hz, 1H), 4.52 (dd, *J* = 6.3, 0.9 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 2.29-2.18 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.3, 155.5, 147.6, 134.9, 124.4, 121.8, 68.1, 60.1, 54.6, 31.2, 30.4, 14.1. HRMS: Calcd. for $C_{12}H_{18}O_5$(M+1): 243.1232, Found: 243.1233. FTIR (neat): 3957, 1748, 1673, 1633, 1444 cm^{-1}.



5.12

This substrate was isolated as a 9:1 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

8-Methoxycarbonyloxy-octa-2,6-dienethioic acid S-ethyl ester (**5.12**). ^{1}H NMR (300 MHz, $CDCl_3$): 6.88-6.81 (m, 1H), 5.78-5.71 (m, 2H), 5.58-5.53 (m, 1H), 4.50 (dd, *J* = 0.9, 6.3 Hz, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 2.25-2.15 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.7, 155.8, 147.9, 135.3, 124.7, 122.1, 66.4, 60.4, 54.9, 31.5, 30.7, 14.4. HRMS: Calcd. for $C_{12}H_{18}O_4S$(M+1): 259.1004, Found: 259.1009. FTIR (neat): 3957, 1748, 1673, 1633, 1444 cm^{-1}.



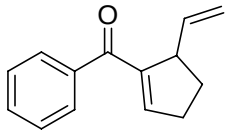
5.5a

This substrate was isolated as a 6:1 mixture of alkene isomers at the position of the allylic carbonate. Spectral data for the major isomer is reported.

Carbonic acid methyl ester 9-oxo-9-phenyl-nona-2,7-dienyl ester (**5.5a**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.91-7.87 (m, 2H), 7.54-7.39 (m, 3H), 7.03-6.96 (m, 1H), 6.88-6.82 (m, 1H), 5.82-5.72 (m, 1H), 5.62-5.52 (m, 1H), 4.54 (dd, *J* = 0.75, 6.45 Hz, 2H), 3.73 (s, 3H), 2.32-2.25 (m, 2H), 2.19-2.04 (m, 2H), 1.64-1.54 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 190.6, 155.5, 149.0, 136.0, 132.5, 128.4, 128.4, 126.1, 126.1, 124.0, 68.3, 54.6, 40.0, 31.5, 27.1. HRMS**:** Calcd. for $C_{17}H_{20}O_4$ (M+1): 289.1440, Found: 289.1431.FTIR (neat): 2935, 1748, 1670, 1621, 1447 cm^{-1}.

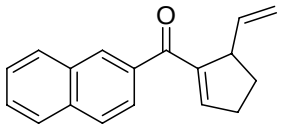
Representative Procedure for Catalytic Enone Cycloallyliation

A solution of mono-enone mono-allylic carboneate **5.2** (0.39 mmol, 100 mol%) in *t*-BuOH (4 mL, 0.1 M) was degassed under vacuum in a sonicator. To this solution was added $Pd(PPh_3)_4$ (18 mg, 0.016 mmol, 1 mol%) and tributylphosphine (0.97 mL, 0.39 mmol, 100 mol%). The reaction was heated to 60 ^oC and allowed to stir for 5 hours at 60 ^oC. The solvent was evaporated *in vacuo* and the reaction was purified by flash chromatography (95:5 Hexane:EtOAc) to afford cycloallylation product **5.3**.



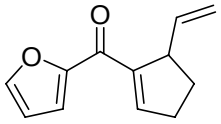
5.3

Phenyl-(5-vinyl-cyclopent-1-enyl)-methanone (**5.3**). ^1H NMR (300 MHz, $CDCl_3$): 7.79-7.75 (m, 2H), 7.56-7.49 (m, 1H), 7.46-7.40 (m, 2H), 6.51 (dt, *J* = 2.6, 1.7 Hz, 1H), 5.91 (ddd, *J* = 17.1, 10.1, 7.3 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.4 Hz, 1H), 4.99 (ddd, *J* = 10.3, 1.5, 0.9 Hz, 1H), 3.87 (q, *J* = 6.7 Hz, 1H), 2.75-2.62 (m, 1H), 2.58-2.45 (m, 1H), 2.33-2.21 (m, 1H), 1.92-1.82 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 193.9, 146.3, 140.0, 139.1, 132.2, 129.2, 128.4, 114.4, 48.7, 32.9, 30.4. HRMS Calcd. for $C_{14}H_{14}O$ (M+1): 199.1123, Found: 199.1130. FTIR (neat): 3061, 2930, 1642, 1353, 1288, 911, 760 cm^{-1}.



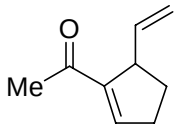
5.13

Naphthalen-2-yl-(5-vinyl-cyclopent-1-enyl)-methanone (**5.13**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.28 (d, *J* = 0.7 Hz, 1H) 7.94 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.91-7.86 (m, 3H), 7.56 (dtd, *J* = 18.0, 6.8, 1.5 Hz, 2H), 6.58 (dt, *J* = 2.6, 1.7 Hz, 1H), 5.15 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.02 (dt, *J* = 10.3, 1.2 Hz, 1H), 3.94 (q, *J* = 7.2 Hz, 1H), 2.78-2.68 (m, 1H), 2.60-2.51 (m, 1H), 2.37-2.27 (m, 1H), 1.97-1.88 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 193.8, 146.5, 146.3, 140.0, 136.3, 135.4, 132.6, 130.6, 129.5, 128.4, 128.2, 128.0, 126.9, 125.4, 114.5, 48.9, 33.0, 30.4. HRMS Calcd. for $C_{18}H_{16}O$ (M+1): 249.1279, Found: 249.1269. FTIR (neat): 3058, 2956, 2927, 2870, 1643, 1465, 1353, 1288 cm^{-1}.



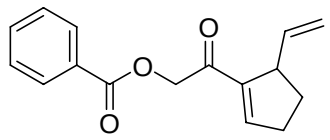
5.14

Furan-2-yl-(5-vinyl-cyclopent-1-enyl)-methanone (**5.14**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.58 (d, *J* = 0.7 Hz, 1H), 7.16 (dd, *J* = 4.1, 0.7 Hz, 1H), 7.00 (dd, *J* = 4.1, 2.4 Hz, 1H), 6.51 (dt, *J* = 2.1, 1.7 Hz, 1H), 5.86 (ddd, *J* = 17.1, 10.1, 7.5 Hz, 1H), 5.06 (dd, *J* = 17.1, 1.4 Hz, 1H), 4.95 (d, *J* = 10.3 Hz, 1H), 3.86 (q, *J* = 6.2 Hz, 1H), 2.72-2.62 (m, 1H), 2.59-2.49 (m, 1H), 2.26-2.16 (m, 1H), 1.86-1.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 179.5, 153.4, 146.3, 145.4, 145.3, 139.9, 118.3, 114.3, 112.2, 48.5, 33.0, 30.1. HRMS Calcd. for $C_{12}H_{12}O_2$ (M+1): 189.0916, Found: 189.0910. FTIR (neat): 3133, 2942, 1637, 1564, 1467, 1391, 1293 cm^{-1}.



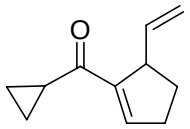
5.15

1-(5-Vinyl-cyclopent-1-enyl)-ethanone (**5.15**). ^{1}H NMR (300 MHz, $CDCl_3$): 6.77-6.75 (m, 1H), 5.88-5.77 (m, 2H), 5.03-4.91 (m, 1H), 3.61-3.58 (m, 1H), 2.61-2.47 (m, 2H), 2.28 (s, 3H), 2.19-2.07 (m, 1H), 1.85-1.76 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 196.1, 147.4, 144.8, 139.8, 113.4, 46.7, 32.0, 30.4, 27.1. HRMS: Calcd. for $C_9H_{12}O$ (M+1): 137.0966, Found: 137.0968. **FTIR** (neat): 2938, 1668, 1611, 1368 cm^{-1}.



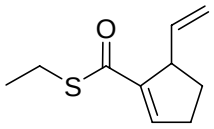
5.16

Benzoic acid 2-oxo-2-(5-vinyl-cyclopent-1-enyl)-ethyl ester (**5.16**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (dd, *J* = 7.2, 0.7 Hz, 2H), 7.57 (dt, *J* = 7.4, 0.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 2.4 Hz, 1H), 5.84 (ddd, *J* = 17.1, 10.1, 7.5 Hz, 1H), 5.21 (ddd, *J* = 59.2, 15.9, 0.7 Hz, 2H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.00 (dt, *J* = 10.3, 0.7 Hz, 1H), 3.70 (q, *J* = 1.4 Hz, 1H), 2.70-2.59 (m, 1H), 2.58-2.49 (m, 1H), 2.24-2.13 (m, 1H), 1.88-1.80 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 190.0, 166.0, 144.9, 144.0, 139.3, 133.2, 129.9, 129.4, 128.4, 114.2, 66.4, 47.3, 32.4, 30.0. HRMS Calcd. for $C_{16}H_{16}O_3$ (M+1): 257.1178, Found: 257.1181. FTIR (neat): 3061, 2940, 1728, 1687, 1272, 1119, 709 cm^{-1}.



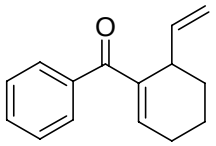
5.17

Cyclopropyl-(5-vinyl-cyclopent-1-enyl)-methanone (**5.17**). ^{1}H NMR (300 MHz, $CDCl_3$): 6.89-6.86 (m, 1H), 5.89-5.77 (m, 1H), 5.03-4.91 (m, 2H), 3.63-3.61 (m, 1H), 2.60-2.47 (m, 2H), 2.33-2.26 (m, 1H), 2.22-2.11 (m, 1H), 1.85-1.62 (m, 1H), 1.05-1.00 (m, 2H), 0.86-0.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 198.2, 147.7, 143.6, 140.1, 113.4, 47.3, 32.1, 30.4, 17.7, 10.9, 10.6. HRMS: Calcd. for $C_{11}H_{14}O$ (M+1): 163.1123, Found: 163.1122. FTIR (neat): 3009, 2942, 1655, 1610, 1445, 1398 cm^{-1}.



5.19

5-Vinyl-cyclopent-1-enecarbothioic acid S-ethyl ester (**5.19**). ^{1}H NMR (300 MHz, $CDCl_3$): 6.83-6.81 (m, 1H), 5.86-5.75 (m, 1H), 5.08-4.95 (m, 2H), 3.68-3.64 (m, 1H), 2.94-2.83 (m, 2H), 2.53-2.42 (m, 2H), 2.24-2.11 (m, 1H), 1.84-1.75 (m, 1H), 1.24 (t, J = 7.5 MHz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 188.8, 146.0, 142.6, 139.4, 114.2, 47.9, 31.7, 30.7, 22.9, 14.8. HRMS: Calcd. for $C_{10}H_{14}OS$ (M+1): 183.0844, Found: 184.0839. FTIR (neat): 2967, 2931, 1659, 1612, 1452 cm^{-1}.



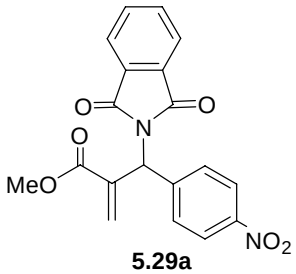
5.20

Phenyl-(6-vinyl-cyclohex-1-enyl)-methanone (**5.20**). ^{1}H NMR (300 MHz, $CDCl_3$): 7.69-7.66 (m, 2H), 7.51-7.36 (m, 3H), 6.5 (t, *J* = 4.05 Hz, 1H), 5.90-5.79 (m, 1H), 5.02-4.94 (m, 2H), 3.6 (s, 1H), 2.35-2.11 (m, 2H), 1.80-1.61 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 197.3, 143.51, 140.3, 140.1, 138.6, 131.6, 129.3, 128.0, 115.1, 36.3, 27.5, 26.1, 17.6. HRMS**:** Calcd. for $C_{15}H_{16}O$ (M+1): 213.1279, Found: 213.1276. FTIR (neat): 2934, 1649, 1446, 1263 cm^{-1}.

5.5.3 Regioselective Allylic Amination of MBH Acetates

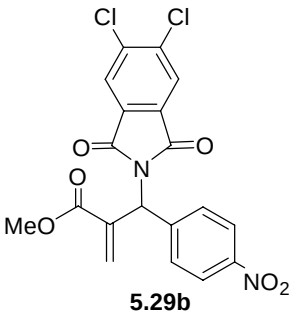
Representative Procedure for Phosphine Catalyzed Allylic Amination of Morita-Baylis-Hillman Acetate

To a THF solution (1.6 mL, 0.3 M) of Morita-Baylis-Hillman acetate (0.5 mmol, 100 mol%) and phthalimide (1.0 mmol, 200 mol%) was added PPh_3 (0.1 mmol, 20 mol%) under Ar. The reaction mixture was stirred at ambient temperature until complete consumption of starting material, at which point the reaction mixture was evaporated onto silica gel and purified *via* silica gel chromatography (4:1 Hexane:EtOAc).



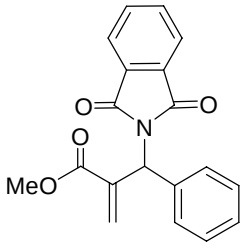
5.29a

2-[(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-(4-nitro-phenyl)-methyl]-acrylic acid methyl ester (**5.29a**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.23-8.19 (m, 2H), 7.87-7.83 (m, 2H), 7.78-7.74 (m, 2H), 7.63-7.60 (m, 2H), 6.64 (d, *J* = 1.5 Hz, 1H), 6.52 (s, 1H), 5.67 (d, *J* = 1.5 Hz, 1H), 3.72(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 165.5, 147.6, 144.0, 136.3, 134.4, 131.5, 129.8, 129.6, 123.8, 123.6, 53.7, 52.4. HRMS Calcd. for $C_{19}H_{15}N_2O_6$(M+1) 367.093011, found 367.091940. FTIR (neat): 3081, 2953, 1722, 1608, 1522, 1384, 1348, 1266, 1144, 1104, 900, 858, 818, 723 cm^{-1}.MP : 162~163 ºC



5.29b

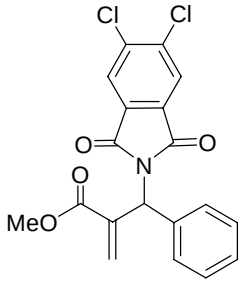
2-[(5,6-Dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-(4-nitro-phenyl)-methyl]-acrylic acid methyl ester (**5.29b**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.23-8.20 (m, 2H), 7.93 (d, J = 0.6 Hz, 2H), 7.60-7.57 (m, 2H), 6.63 (d, J = 1.2 Hz, 1H), 6.46 (s, 1H), 5.62 (d, J = 1.8 Hz, 1H), 3.73 (d, J = 0.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.7, 165.4, 147.7, 143.5, 139.5, 135.9, 130.5, 130.2, 129.6, 125.7, 123.9, 54.2, 52.4. HRMS Calcd. for $C_{19}H_{13}N_2O_6Cl_2$ (M+1): 435.015067, found 435.014595. FTIR (neat): 3095, 2925, 1723, 1524, 1377, 1346, 1144, 1104, 910, 733 cm^{-1}. MP : 175 – 176 ^{o}C



5.30a

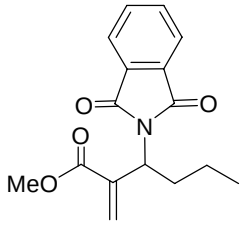
2-[(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-phenyl-methyl]-acrylic acid methyl ester (**5.30a**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.85-7.79 (m, 2H), 7.72-7.68 (m, 2H), 7.45-7.43 (m, 2H), 7.37-7.26 (m, 3H), 6.56 (s, 1H), 6.40 (s, 1H), 5.63 (d, J = 1.8 Hz, 1H), 3.70 (d, J = 0.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 167.8, 166.0, 137.4, 136.9, 133.9, 131.7, 129.5, 128.5, 128.0, 123.3, 54.5, 52.1. HRMS Calcd. for $C_{19}H_{16}NO_4$ (M+1): 322.1079,

Found: 322.1086. FTIR (neat): 3064, 2952, 1770, 1727, 1632, 1386, 1356, 1331, 1265, 1142, 1113, 942, 891, 721 cm-1. MP : 109 - 110 ^{o}C



5.30b

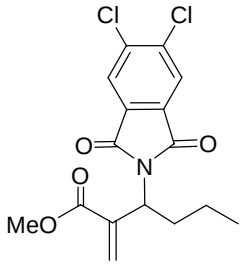
2-[(5,6-Dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-phenyl-methyl]-acrylic acid methyl ester (**3.30b**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.90 (d, *J* = 0.9 Hz, 2H), 7.43-7.28 (m, 5H), 6.56 (d, *J* = 1.5 Hz, 1H), 6.32 (s, 1H), 5.59 (d, *J* = 2.1 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 165.9, 165.9, 138.9, 137.0, 136.5, 130.8, 130.0, 128.7, 128.5, 128.3, 125.4, 55.1, 52.2. HRMS Calcd. for $C_{19}H_{14}NO_4Cl_2$ (M+1): 390.0300, Found: 390.0300. FTIR (neat): 3032, 2953, 1779, 1722, 1438, 1382, 1354, 1265, 1191, 1143, 1104, 910, 733 cm-1. MP : 117 - 118 ^{o}C



5.31a

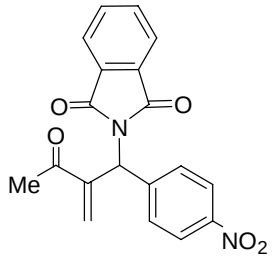
3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-methylene-hexanoic acid methyl ester (**5.31a**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.85-7.79 (m, 2H), 7.74-7.67 (m, 2H), 6.53 (s, 1H), 6.08 (d, *J* = 1.5 Hz, 1H), 5.29-5.23 (m, 1H), 3.71 (s, 3H), 2.37-2.29 (m, 1H), 1.98-1.84

(m, 1H), 1.40-1.25 (m, 2H), 0.94 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 168.0, 166.3, 137.5, 133.8, 131.7, 128.0, 123.1, 52.0, 49.3, 31.9, 19.6, 13.5. HRMS Calcd. for $C_{16}H_{18}NO_4$ (M+1): 288.1236, Found: 288.1249. FTIR (neat): 2959, 2931, 1773, 1720, 1466, 1438, 1386, 1356, 1297, 1135, 1082, 962, 925, 718 cm^{-1}.



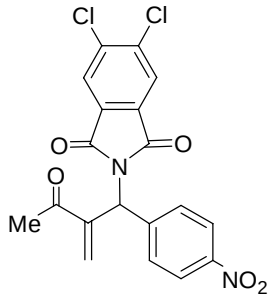
5.31b

3-(5,6-Dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-methylene-hexanoic acid methyl ester (**5.31b**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.89 (s, 2H), 6.54 (s, 1H), 6.08 (d, J = 1.2 Hz, 1H), 5.24-5.19 (m, 1H), 3.70 (s, 3H), 2.37-2.21 (m, 1H), 1.95-1.84 (m, 1H), 1.37-1.25 (m, 2H), 0.94(t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 166.1, 165.9, 138.8, 136.9, 130.8, 128.5, 125.3, 52.0, 49.7, 31.7, 19.5, 13.5. HRMS Calcd. for $C_{16}H_{16}NO_4Cl_2$ (M+1): 356.0456, Found: 356.0456. FTIR (neat): 3096, 2960, 2874, 1778, 1723, 1633, 1439, 1377, 1297, 1195, 1141, 1086, 961, 911, 815, 776, 745, 633, 602 cm^{-1}. MP : 110 - 111 ^oC



5.32a

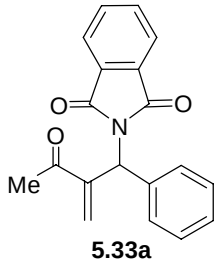
2-[2-Methylene-1-(4-nitro-phenyl)-3-oxo-butyl]-isoindole-1,3-dione (**5.32a**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.19 (d, *J* = 11.6 Hz, 2H), 7.81 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.71 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.54 (d, *J* = 11.6 Hz, 2H), 6.50 (s, 1H), 6.41 (s, 1H), 5.74 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 197.7, 167.7, 147.5, 145.0, 144.6, 134.4, 131.5, 129.5, 123.8, 123.6, 53.1, 26.0. HRMS Calcd. for $C_{19}H_{15}N_2O_5$ (M+1): 351.0981, Found: 351.0981. FTIR (neat): 3081, 1772, 1716, 1680, 1606, 1521, 1384, 1348, 1107, 1086, 722 cm^{-1}. MP : 137 – 139 ^{o}C



5.32b

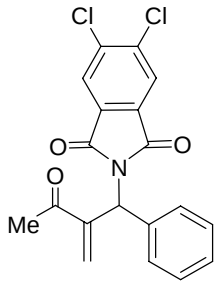
5,6-Dichloro-2-[2-methylene-1-(4-nitro-phenyl)-3-oxo-butyl]-isoindole-1,3-dione (**5. 32b**). ^{1}H NMR (400 MHz, $CDCl_3$): 8.19 (d, *J* = 8.2 Hz, 2H), 7.88 (s, 2H), 7.52 (d, *J* = 8.8 Hz, 2H),6.42 (dd, *J* = 5.0, 1.2 Hz, 2H), 5.68 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 197.7, 169.9, 147.7, 144.7, 144.1, 139.4, 130.6, 129.8, 129.5, 125.7, 124.0, 53.6, 25.9. HRMS Calcd. for $C_{19}H_{13}N_2O_5Cl_2$ (M+1): 419.0201, Found: 419.0190.

FTIR (neat): 3094, 1779, 1719, 1679, 1603, 1523, 1345, 1102, 909, 868, 736 cm^{-1}. MP : 176 – 177 ^{o}C



5.33a

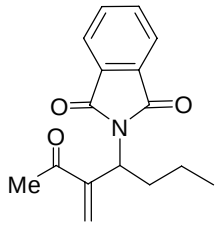
3,4-Dimethyl-1-(2-methylene-3-oxo-1-phenyl-butyl)-pyrrole-2,5-dione (**5.33a**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.65 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.38 – 7.24 (m, 5H), 6.35 (d, *J* = 1.6 Hz, 1H), 6.32 (d, *J* = 1.6 Hz, 1H), 5.67 (d, *J* = 2.0 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 198.3, 168.0, 146.3, 137.4, 133.9, 131.7, 129.0, 128.6, 128.5, 128.0, 123.3, 53.9, 26.1. HRMS Calcd. for $C_{19}H_{16}NO_3$ (M+1): 306.1130, Found: 306.1129. FTIR (neat): 3062, 1769, 1714, 1679, 1387, 1360, 1330, 1112, 1074, 720 cm^{-1}. MP : 117 - 118 ^{o}C



5.33b

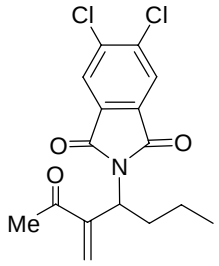
5,6-Dichloro-2-(2-methylene-3-oxo-1-phenyl-butyl)-isoindole-1,3-dione (**5.33b**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.85 (s, 2H), 7.34 – 7.29 (m, 5H), 6.33 (d, *J* = 1.6 Hz, 1H), 6.28 (t, *J* = 1.8 Hz, 1H), 5.65 (d, *J* = 1.6 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$): 198.3, 166.1, 145.9, 138.9, 137.0, 130.9, 129.6, 128.8, 128.5, 128.2, 125.4, 54.5, 26.0. HRMS Calcd. for $C_{19}H_{14}NO_3Cl_2$ (M+1): 374.0351, Found: 374.0359. FTIR (neat): 3065, 2923, 1778, 1717, 1680, 1382, 1353, 1142, 1115, 740 cm^{-1}. MP : 95 - 96 ^oC



5.34a

2-(2-Methylene-3-oxo-1-propyl-butyl)-isoindole-1,3-dione (**5.34a**). ^1H NMR (400 MHz, $CDCl_3$): 7.82 – 7.68 (m, 2H), 7.71 – 7.68 (m, 2H), 6.34 (s, 1H), 6.26 (d, *J* = 0.8 Hz, 1H), 5.34 (dd, *J* = 5.2, 4.8 Hz, 1H), 2.33 (s, 3H), 2.30 – 2.22 (m, 1H), 1.86 – 1.78 (m, 1H), 1.36 -1.27 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 198.3, 168.2, 146.1, 133.9, 131.8, 127.8, 123.9, 48.4, 32.3, 26.1, 19.7, 13.6. HRMS Calcd. for $C_{16}H_{18}NO_3$ (M+1): 272.1287, Found: 272.1289. FTIR (neat): 2961, 2873, 1778, 1718, 1680, 1381, 1357, 744 cm^{-1}.



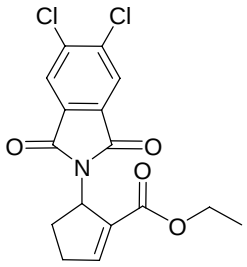
5.34b

5,6-Dichloro-2-(2-methylene-3-oxo-1-propyl-butyl)-isoindole-1,3-dione (**5.34b**). ^1H NMR (400 MHz, $CDCl_3$): 7.87 (s, 2H), 6.36 (s, 1H), 6.26 (d, *J* = 1.2 Hz, 1H), 5.28 (dd, *J*

= 11.6, 4.8 Hz, 1H), 2.32 (s, 3H), 2.26 – 2.16 (m, 1H), 1.85 – 1.77 (m, 1H), 1.34 -1.23 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 198.21, 166.11, 145.5, 138.8, 130.9, 128.3, 125.3, 48.7, 32.0, 26.0, 19.6, 13.6. HRMS Calcd. for $C_{16}H_{16}NO_4Cl_2$ (M+1): 340.0507, Found: 340.0518. FTIR (neat): 2961, 2873, 1778, 1718, 1680, 1610, 1381, 1357, 1193, 744 cm^{-1}. MP : 102 - 103 ^oC

Representative Procedure for Phosphine Catalyzed Allylic Amination of of β-substituted Morita-Baylis-Hillman acetate

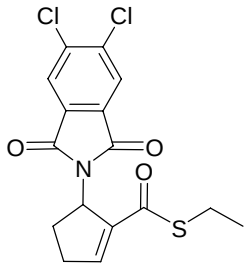
To a THF solution (1.6 mL, 0.3 M) of β-substituted Morita-Baylis-Hillman acetate **7** (0.5 mmol, 100 mol%) and 4,5-dichlorophthalimid (1.0 mmol, 200 mol%) was added PBu_3 (0.1 mmol, 20 mol%) under Ar. The reaction mixture was stirred at 60 ^oC until complete consumption of starting material, at which point the reaction mixture was evaporated onto silica gel and purified *via* silica gel chromatography (10:1 Hexane:EtOAc).



5.35b

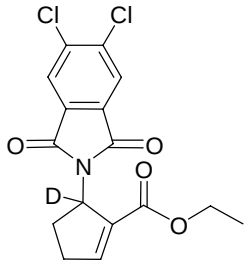
5-(5,6-Dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclopent-1-enecarboxylic acid ethyl ester (**5.35b**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (s, 2H), 7.08 (t, *J* = 2.0 Hz, 1H), 5.54 – 5.50 (m, 1H), 4.11 – 3.97 (m, 2H), 2.97 – 2.88 (m, 1H), 2.58 – 2.44 (m, 2H), 2.19

– 2.11 (m, 1H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.5, 163.5, 148.6, 138.8, 132.3, 131.2, 125.3, 60.3, 54.4, 31.9, 28.9, 14.0. HRMS Calcd. for $C_{16}H_{14}NO_4Cl_2$ (M+1): 354.0300, Found: 354.0291. FTIR (neat): 2981, 1777, 1717, 1639, 1451, 1391, 1360, 1294, 1210, 1105, 742 cm^{-1}. MP : 88 - 89 ^{o}C.



5.36b

5-(5,6-Dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclopent-1-enecarbothioic acid S-ethyl ester (**5.36b**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (s, 2H), 7.08 (d, J = 1.2 Hz, 1H), 5.58 – 5.55 (m, 1H), 2.98 – 2.90 (m, 1H), 2.86 – 2.75 (m, 2H), 2.61 – 2.54 (m, 1H), 2.51 – 2.41 (m, 1H), 2.16 – 2.08 (m, 1H), 1.16 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 187.8, 165.8, 146.6, 139.5, 138.7, 131.1, 125.4, 54.3, 32.1, 28.9, 22.9, 14.6. HRMS Calcd. for $C_{16}H_{14}NO_3SCl_2$ (M+1): 370.0071, Found: 370.0076. FTIR (neat): 2930, 1778, 1717, 1655, 1387, 1358, 1164, 1109, 744 cm^{-1}. MP : 127 - 128 ^{o}C



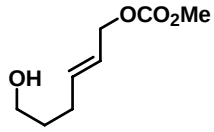
deuterio-5.35b

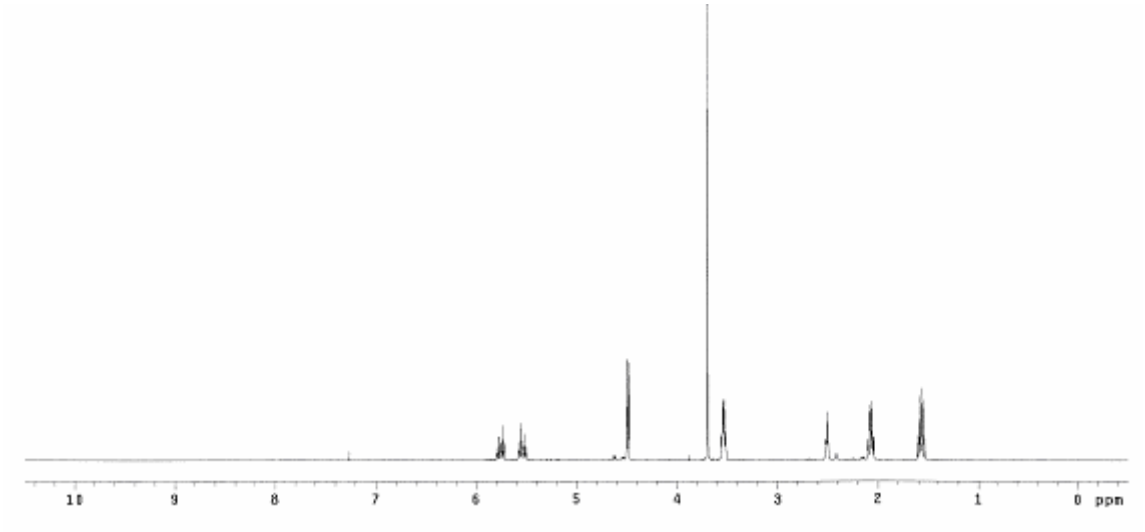
***Deuterio*-5-(5,6-Dichloro-1,3-dioxo-1,3-dihydro-isoindol-2-yl)-cyclopent-1-ene carboxylic acid ethyl ester** (*deuterio*-**5.35b**). ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (s, 2H), 7.08 (t, J = 2.6 1H), 5.95 – 5.55 (m, 0.16H), 4.10- 3.96 (m, 2H), 2.96 – 2.88 (m, 1H), 2.59 – 2.47 (m, 2H), 2.18 – 2.11 (m, 1H), 1.10 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 166.1, 163.7, 148.9, 139.0, 132.5, 131.4, 125.5, 60.6, 32.1, 29.0, 14.3. HRMS Calcd. for $C_{16}H_{13}D_1N_1O_4Cl_2$ (M+1): 355.0362, Found: 355.0372. FTIR (neat): 2980, 1775, 1718, 1637, 1367, 1296, 1191, 1142, 1039, 740 cm^{-1}.

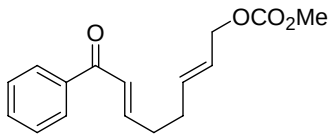
Representative Procedure for Asymmetric Allylic Amination

To a THF solution (1.6 mL, 0.3 M) of Morita-Baylis-Hillman acetate (0.5 mmol, 100 mol%) and phthalimid (1.0 mmol, 200 mol%) was added (*R*)-Cl-MeO-BIPHEP (0.1 mmol, 20 mol%) under Ar, and then the reaction mixture was stirred at 60 ^{o}C until complete consumption of starting material, at which point the reaction mixture was evaporated onto silica gel and purified *via* silica gel chromatography (4:1 Hexane:EtOAc). Yield: 80%. Then enantiomeric purity was determined using a Varian Pro Star HPLC equipped with Chiralcel OD column, eluting with 15% isopropyl alcohol in hexane. Detection wavelength: 220 λ. Flow rate: 0.5 mL/min. 56% ee.

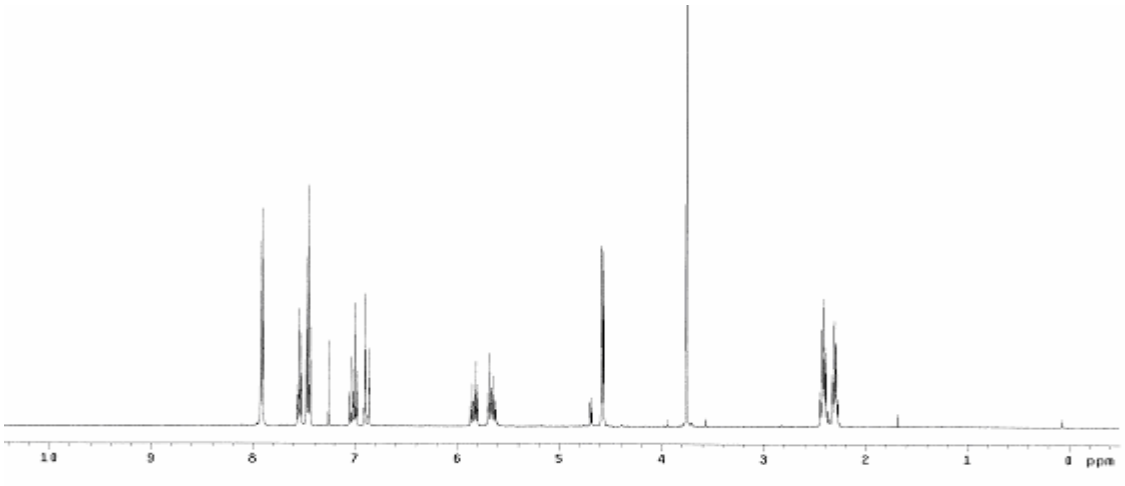
5.6 SPECTRA

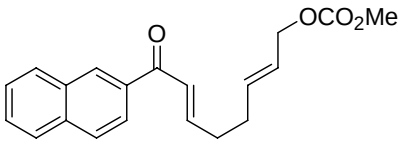




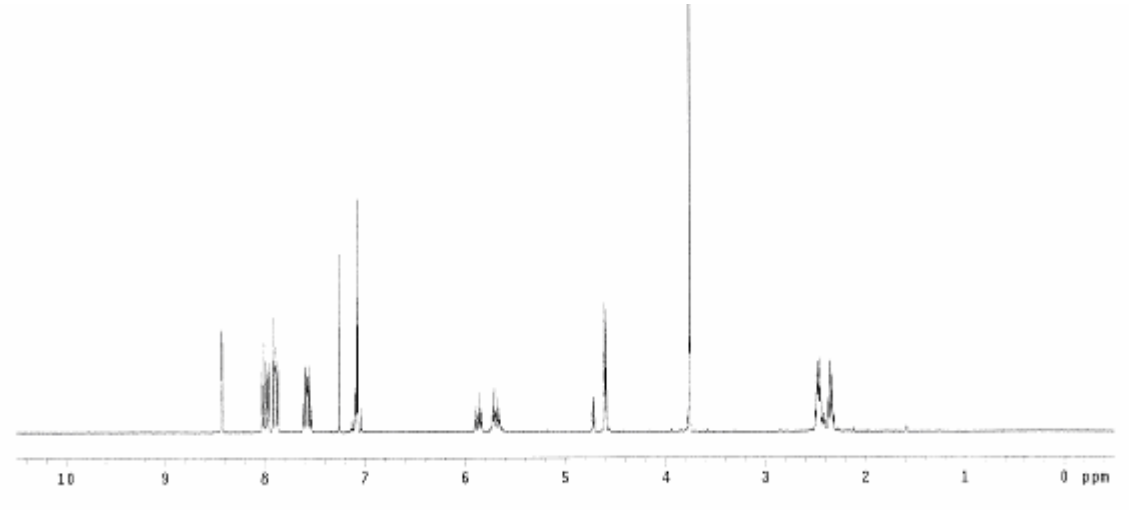


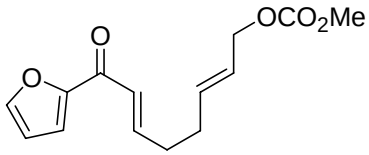
5.5





5.6





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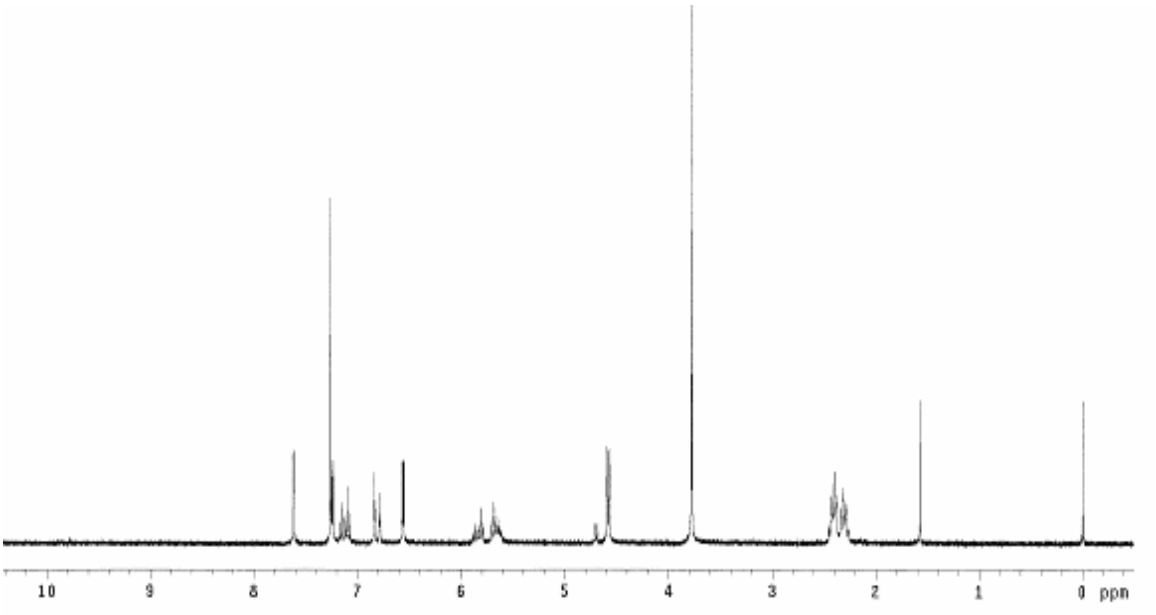

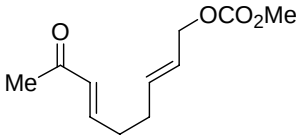

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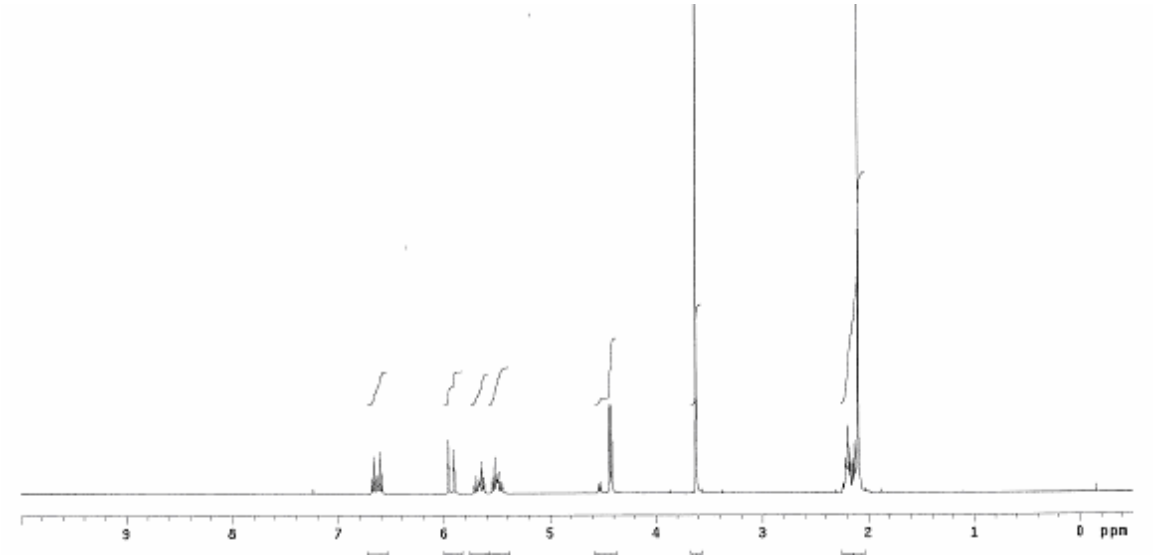
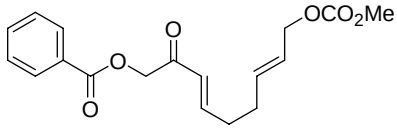
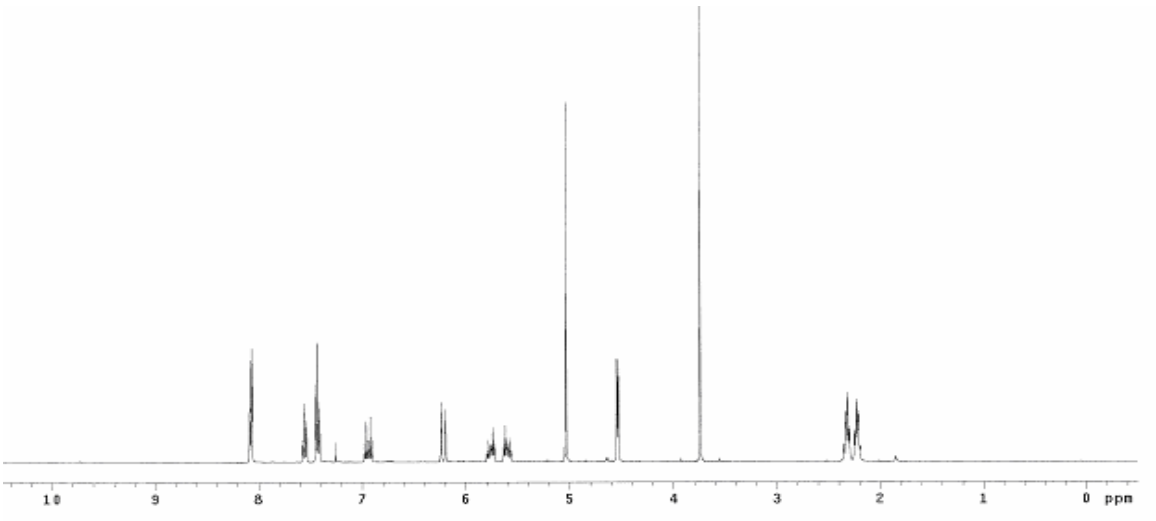
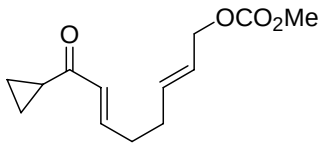


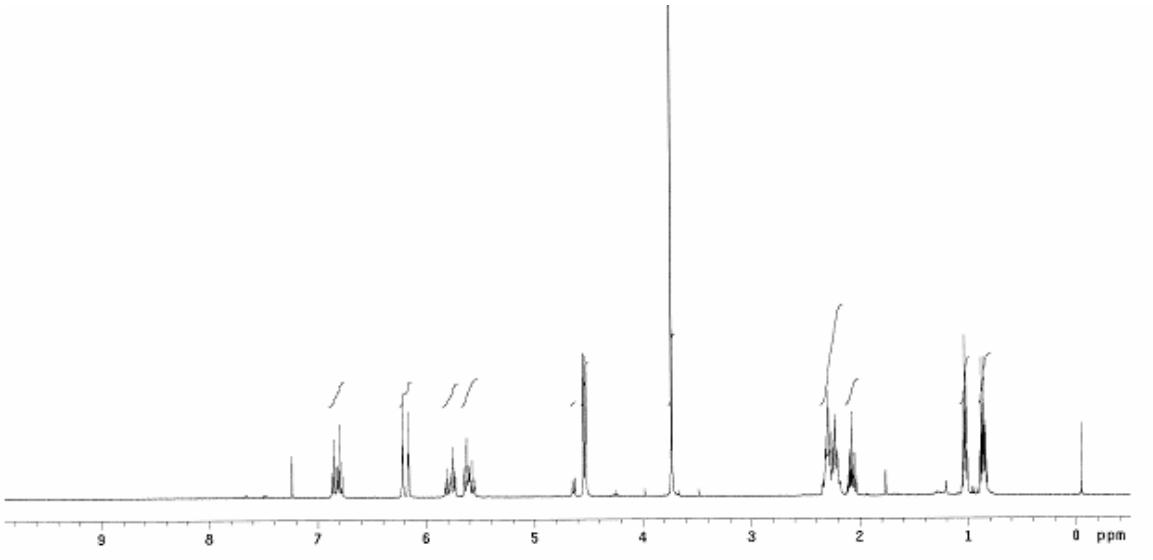


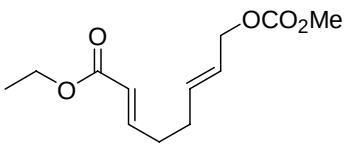
5.9



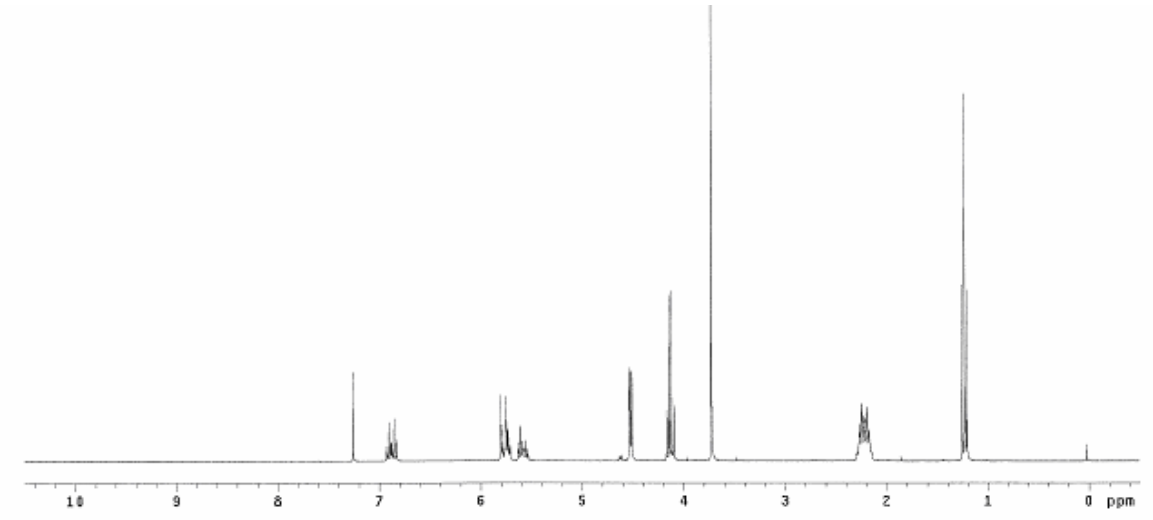


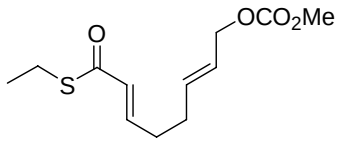
5.10



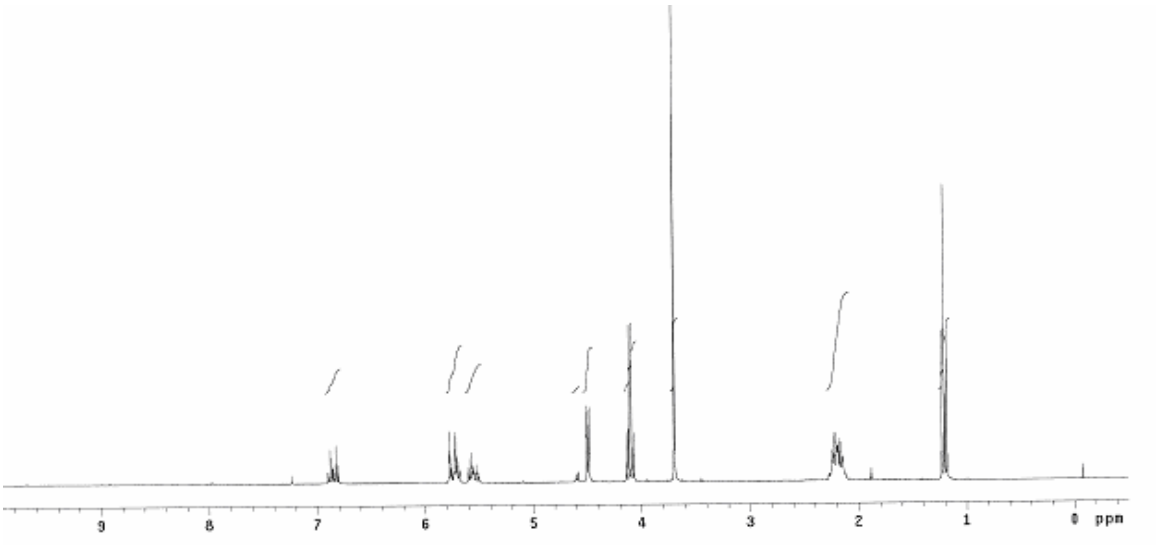


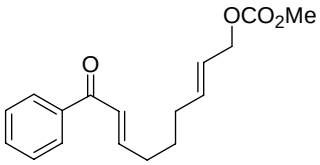
5.11



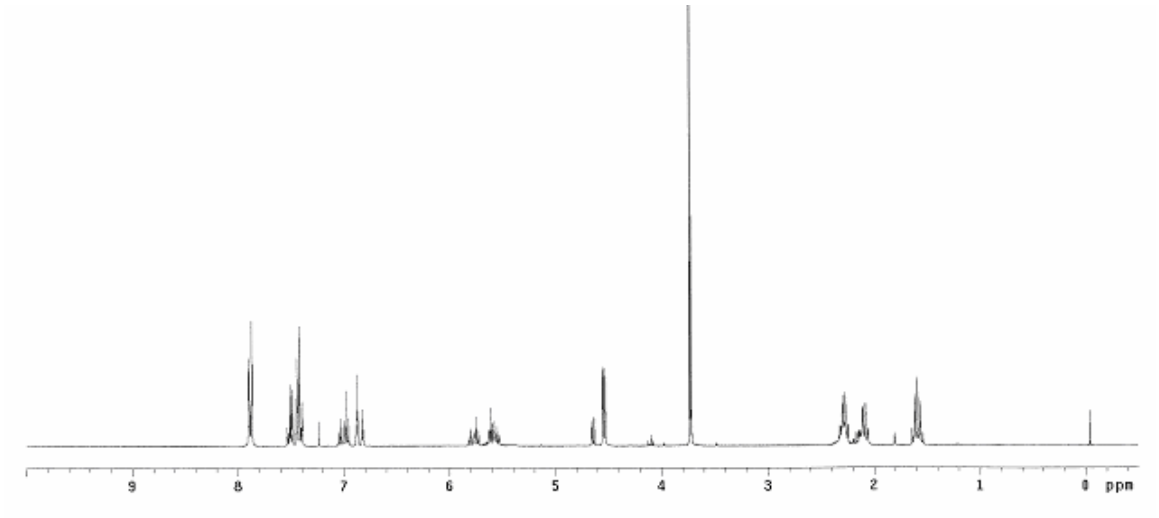


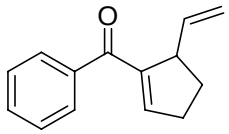
5.12



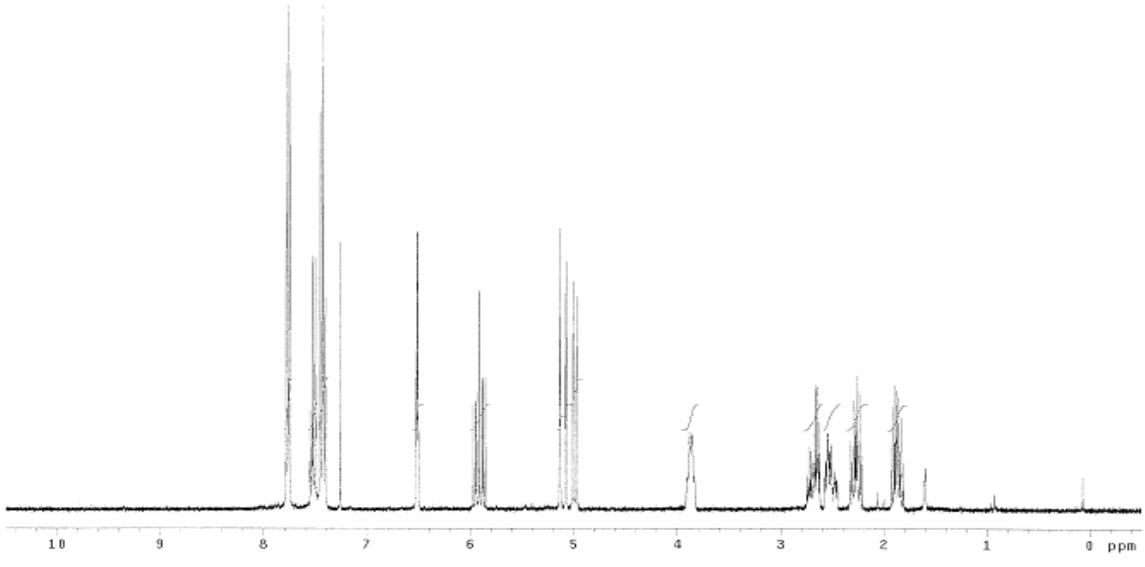


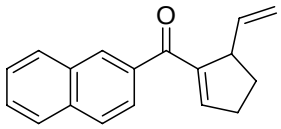
5.5a





5.3





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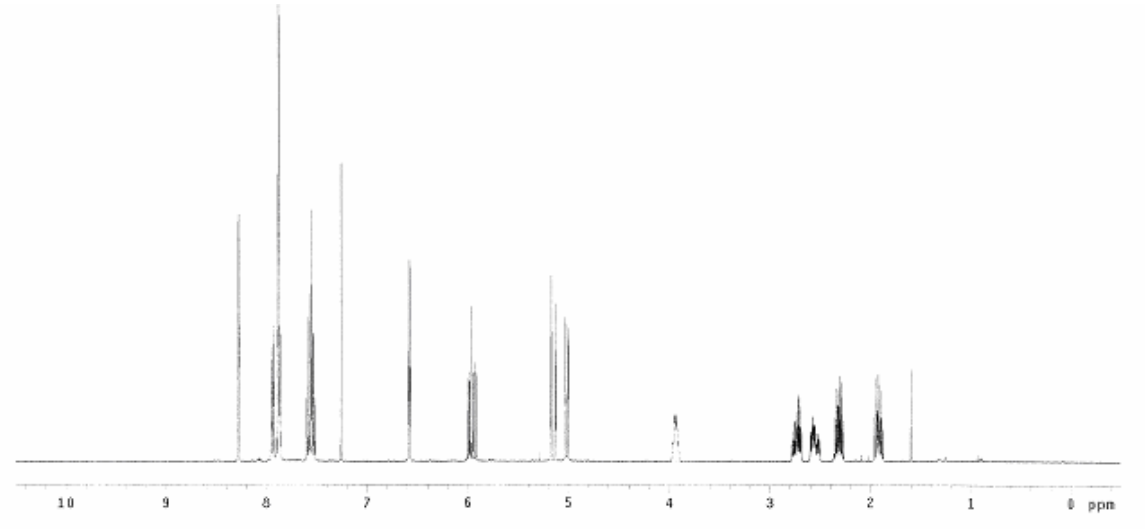

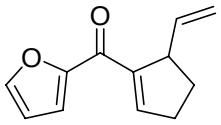

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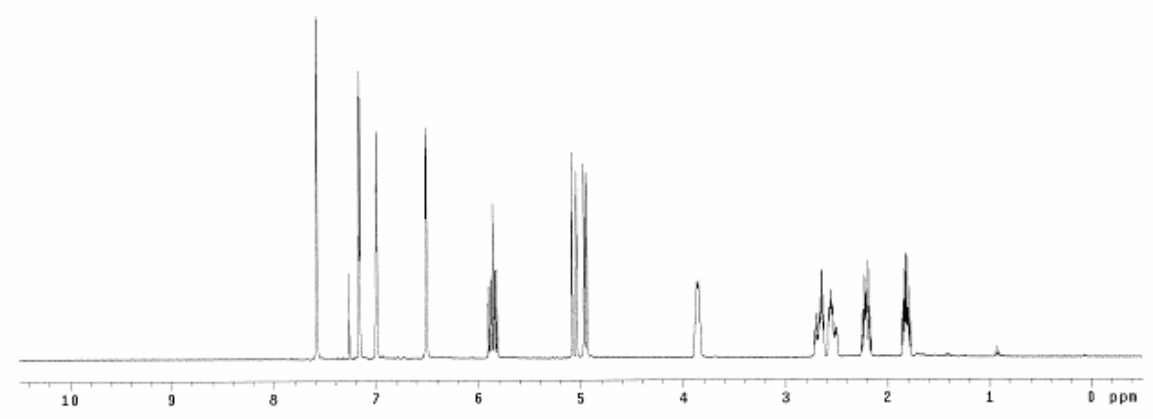

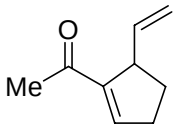

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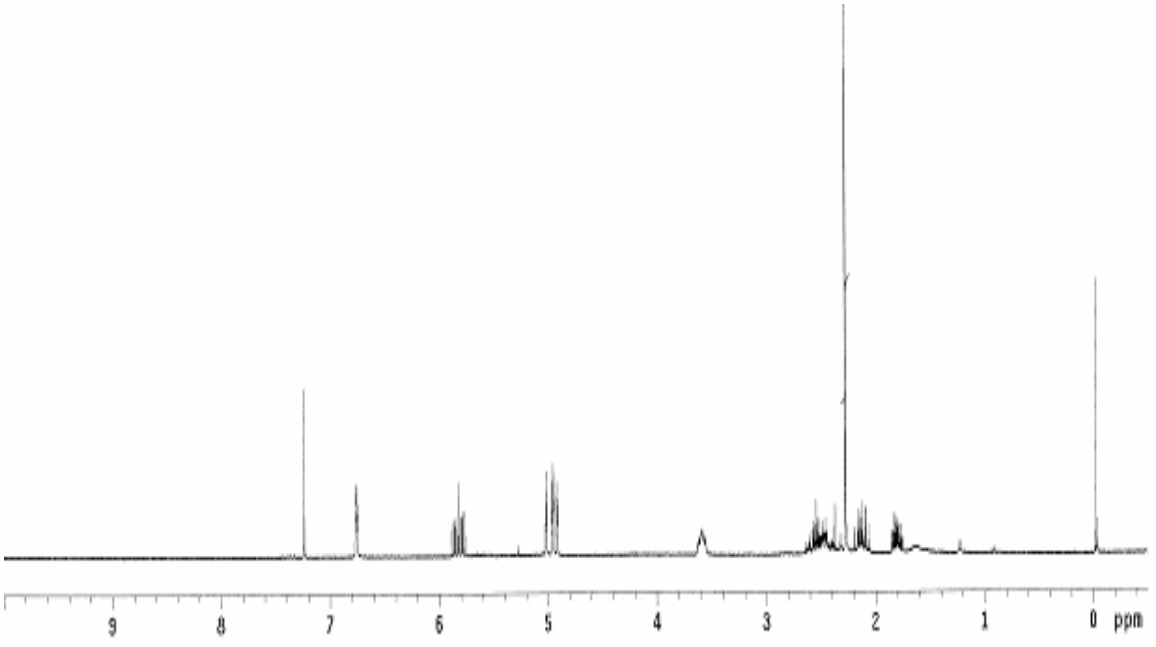

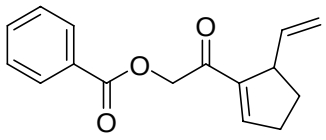

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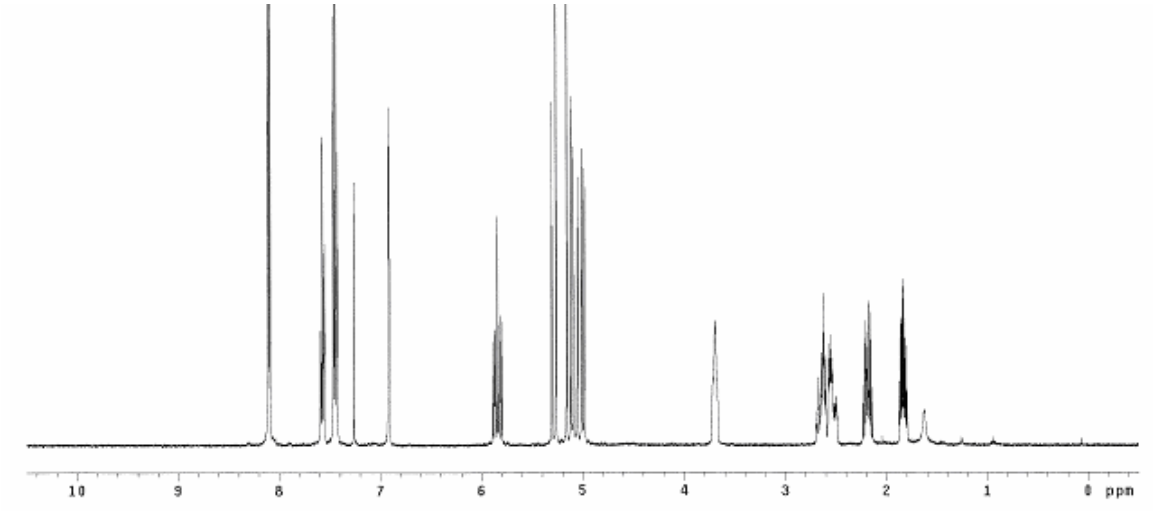

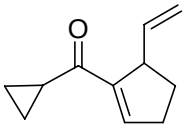

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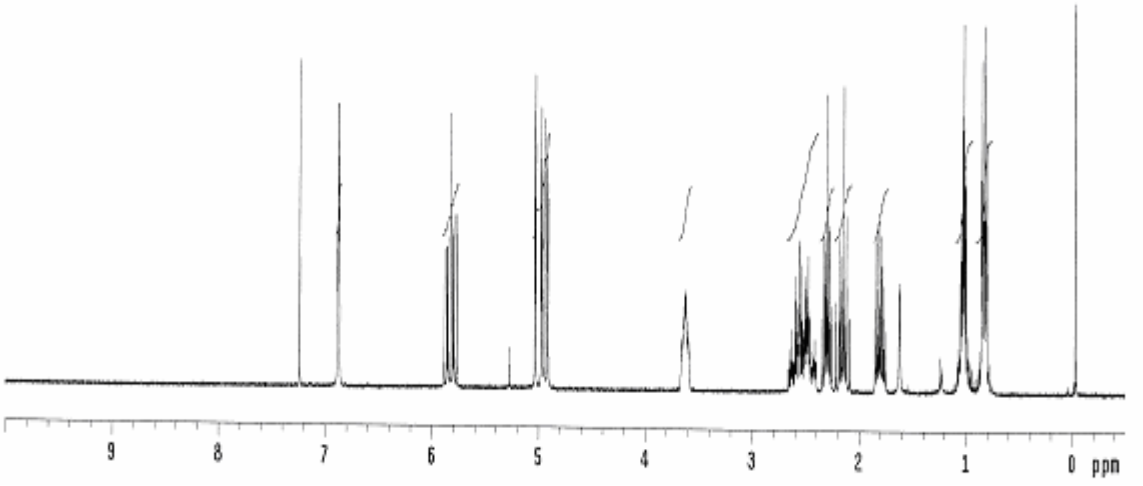

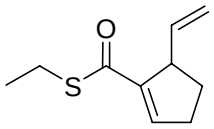

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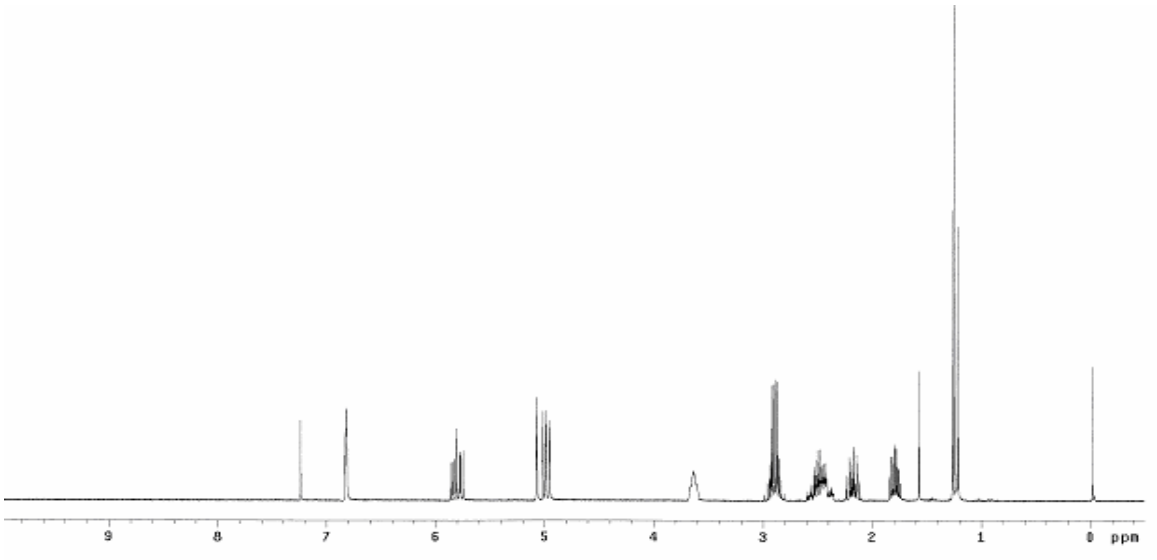

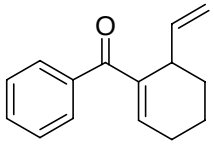

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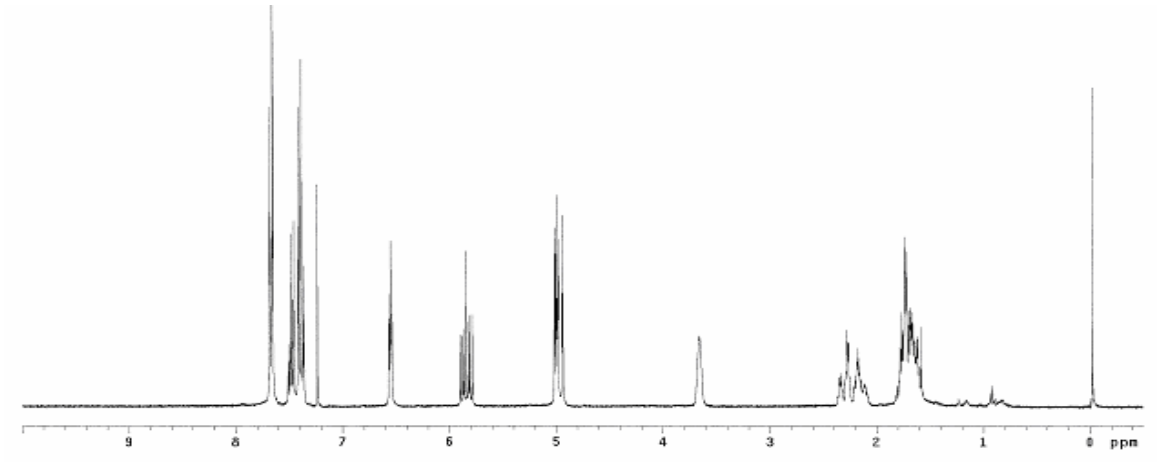

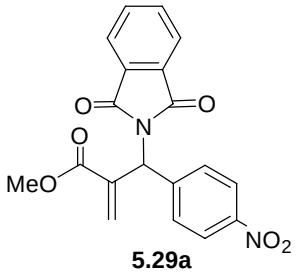
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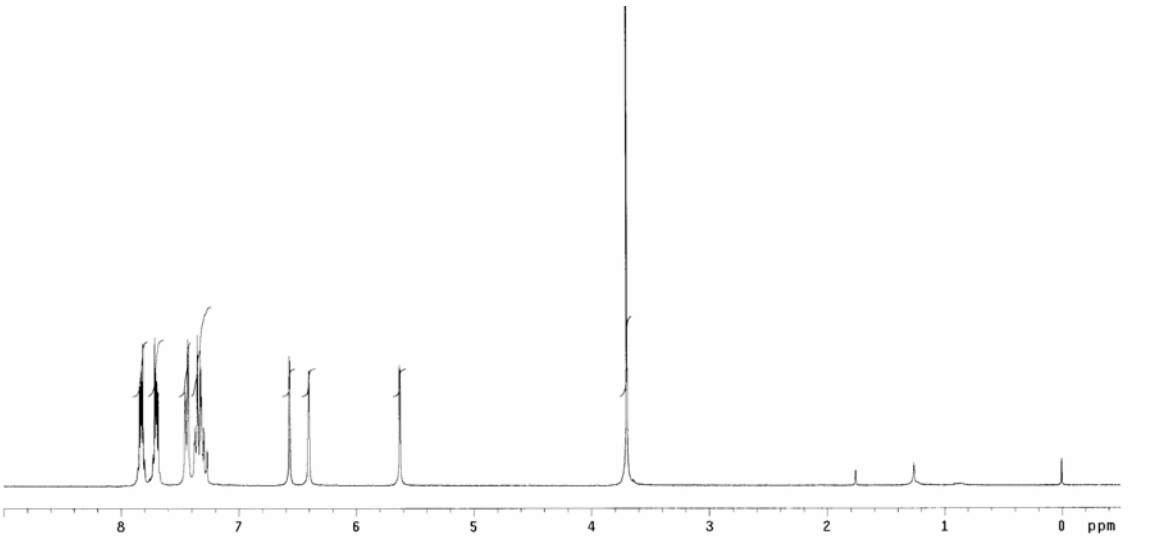
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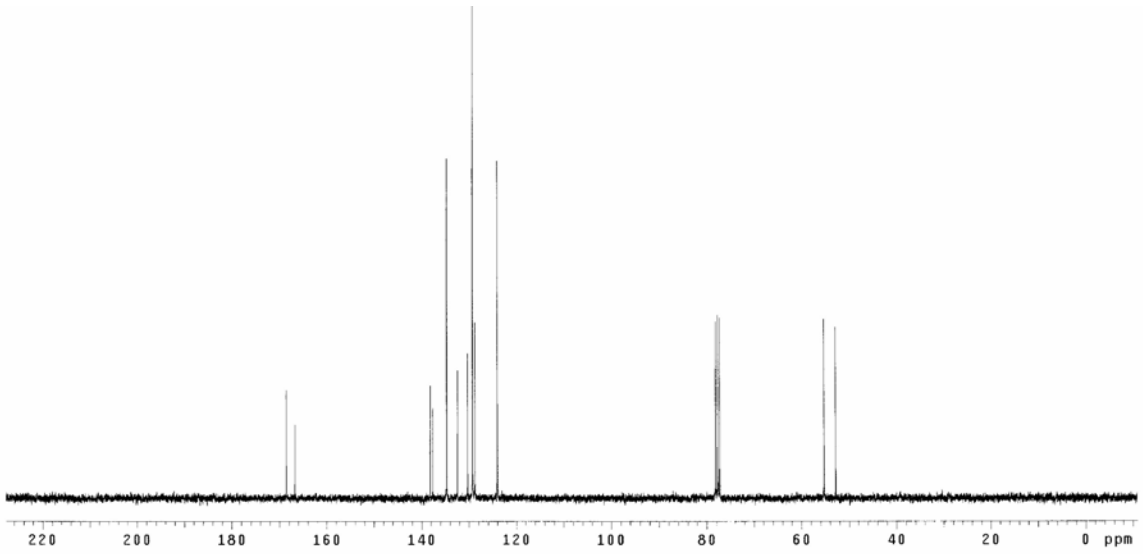
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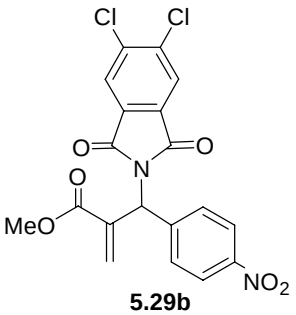
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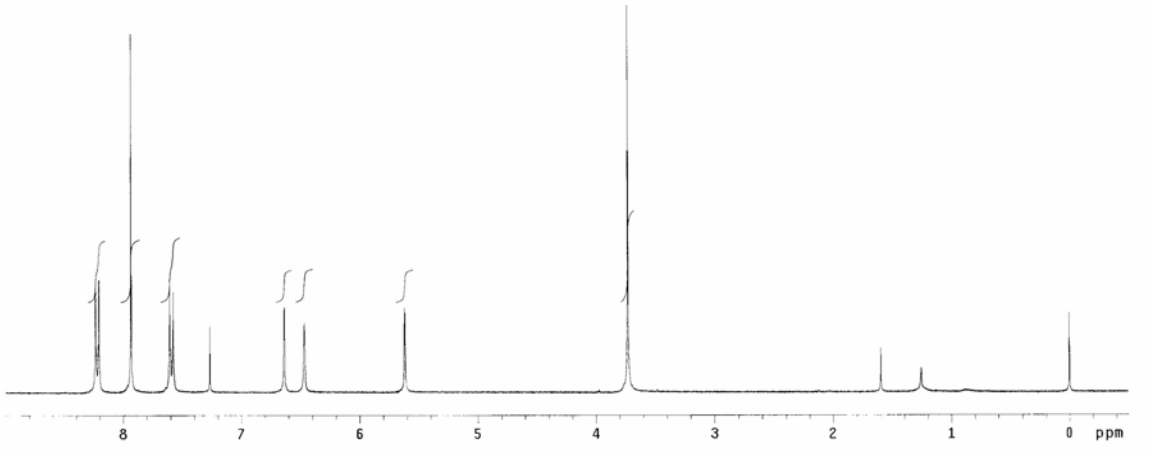
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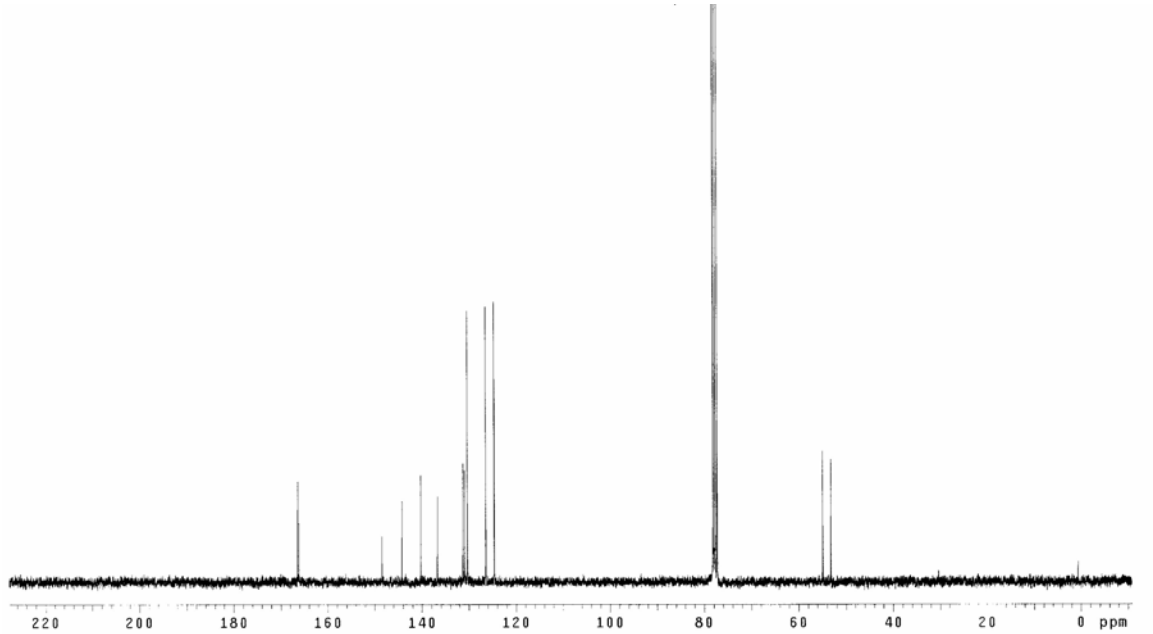
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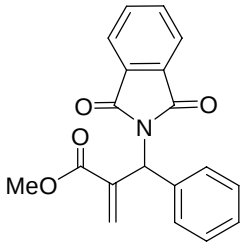
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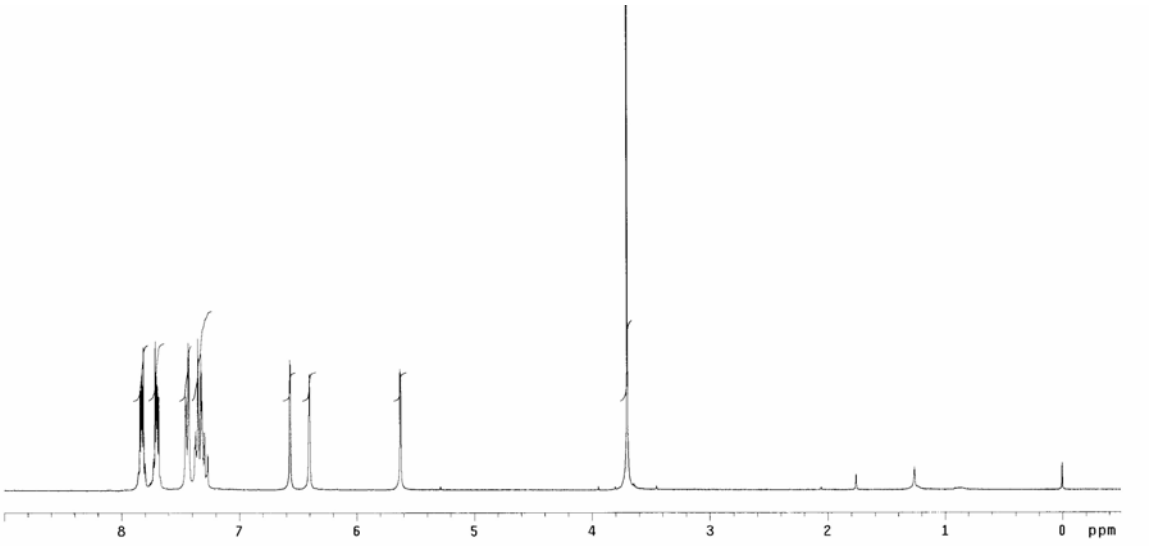
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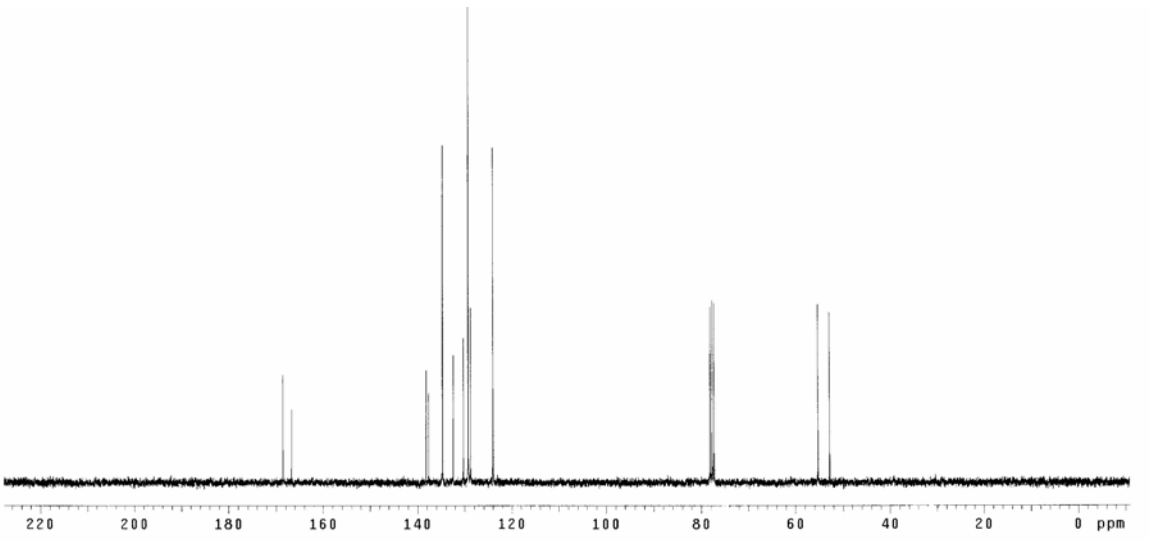
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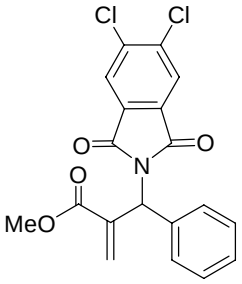
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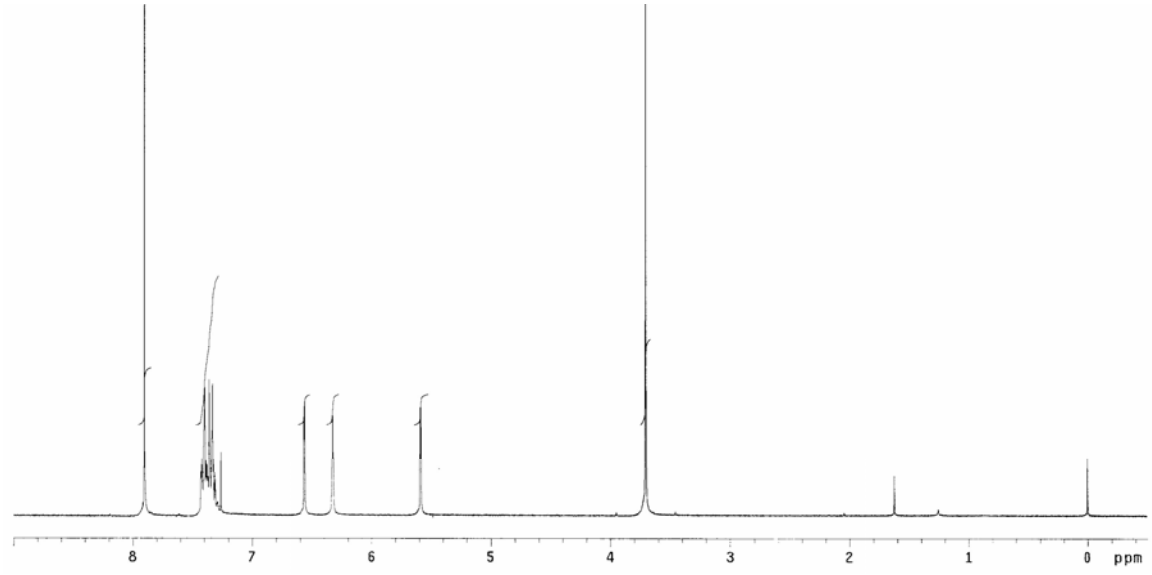
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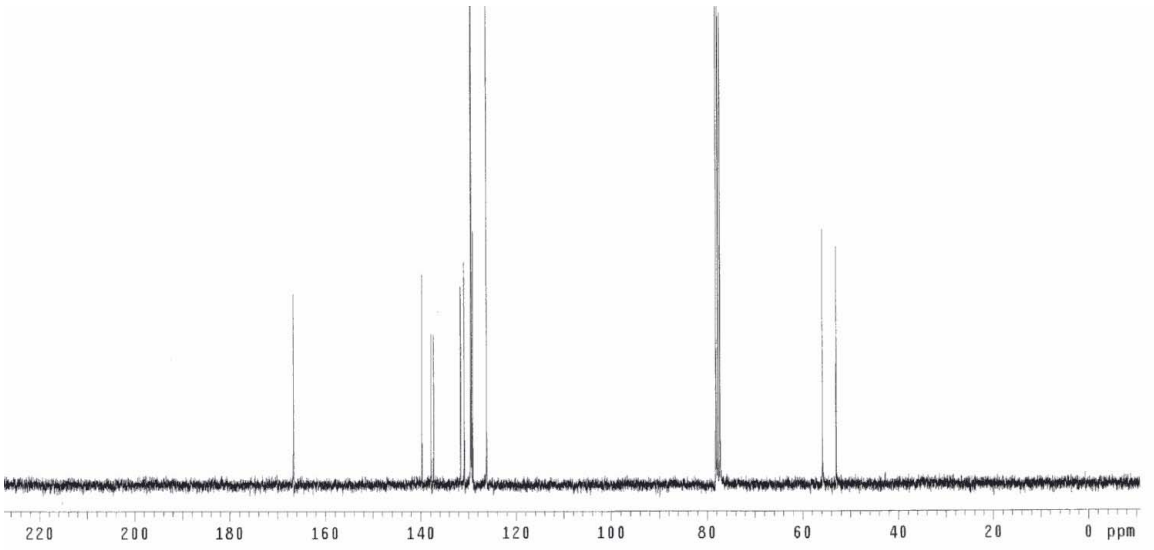
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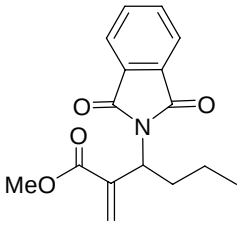
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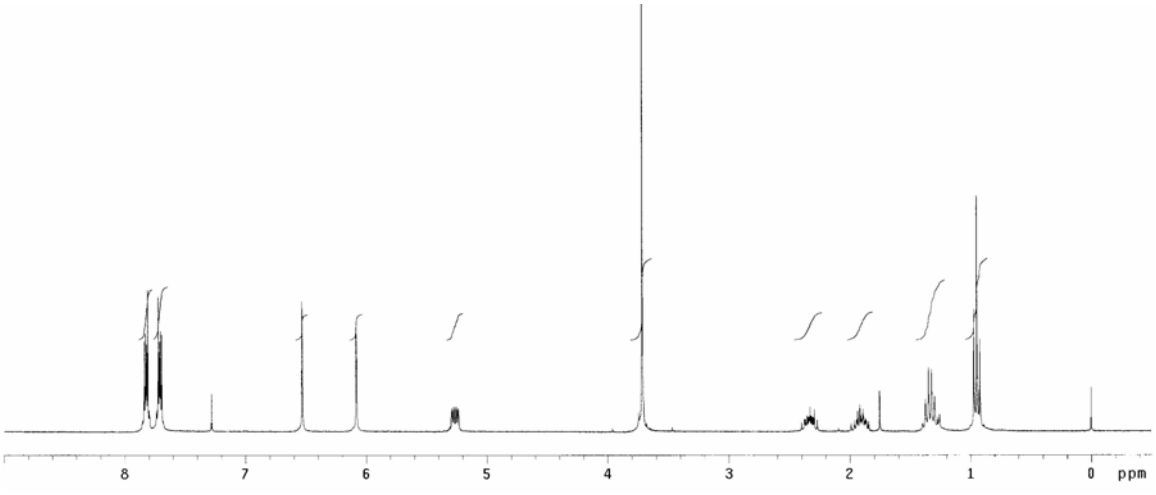
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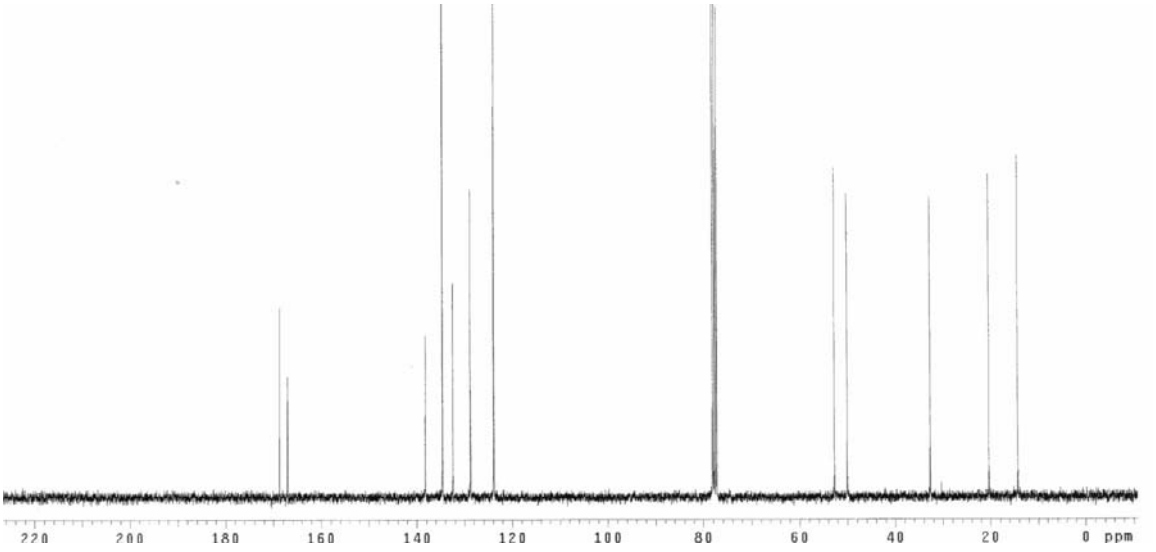
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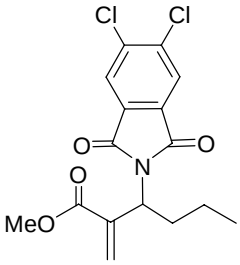
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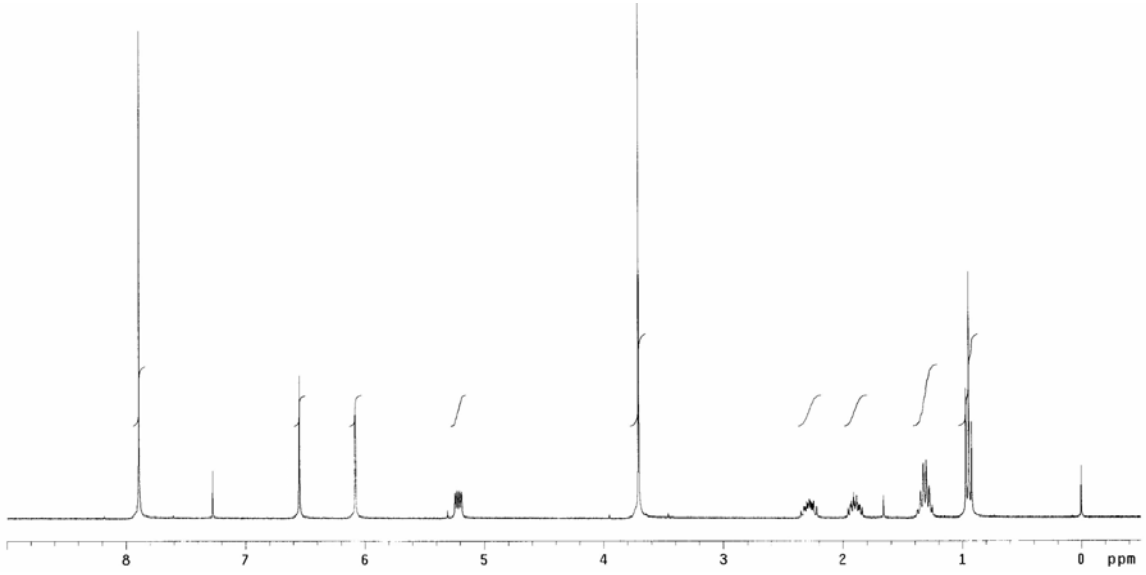
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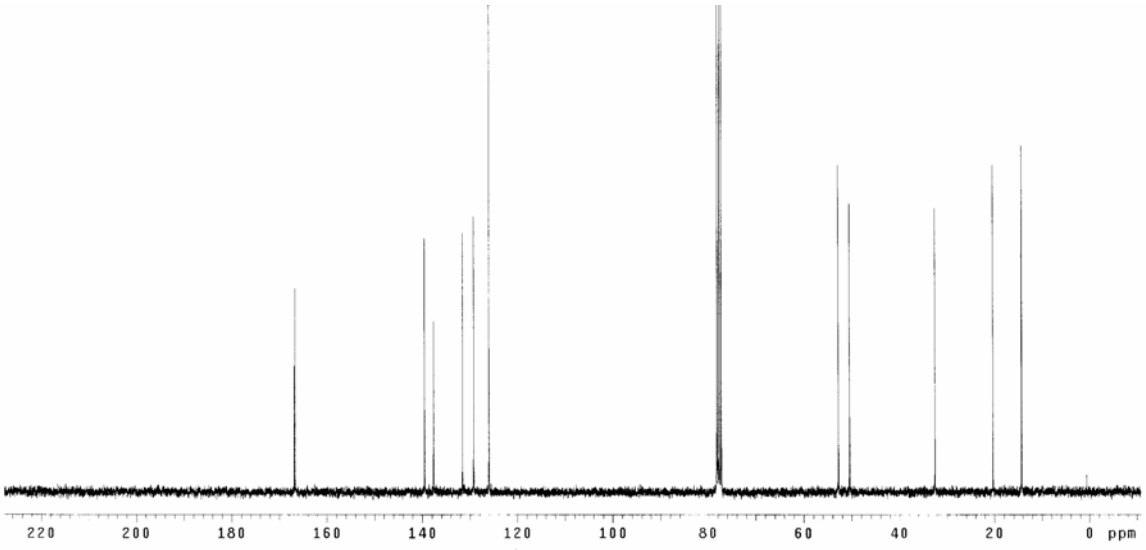
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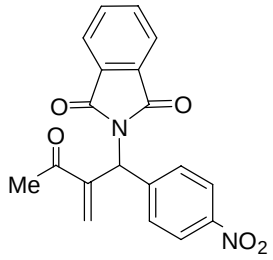
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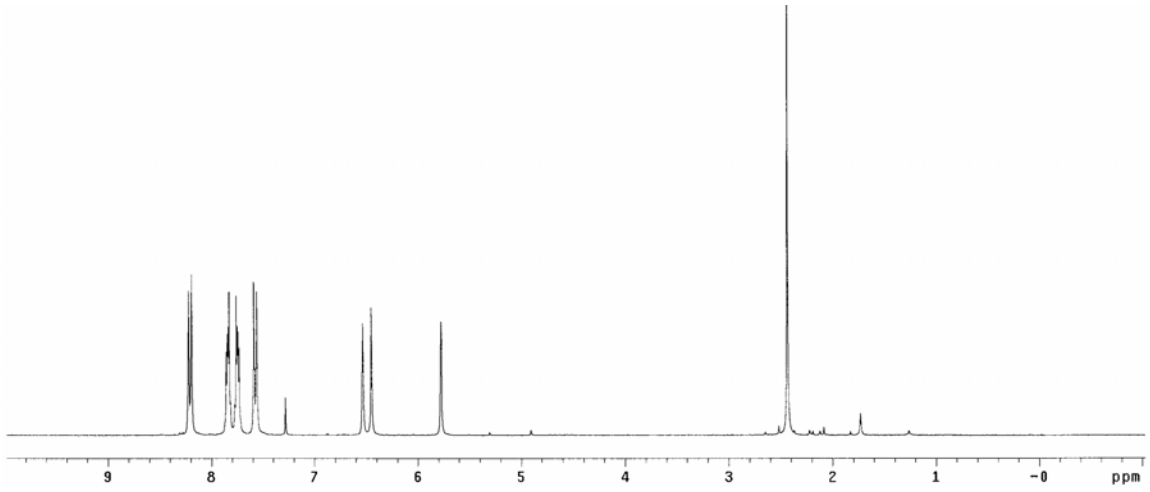
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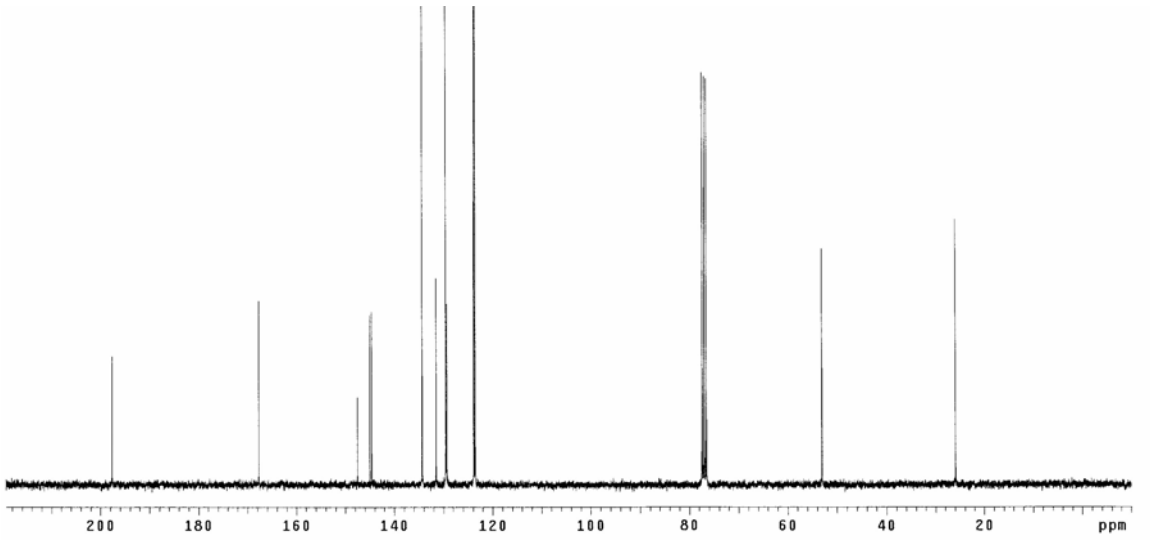
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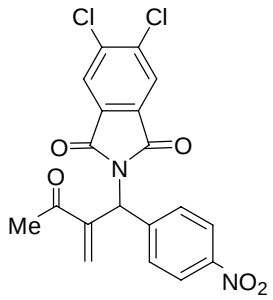
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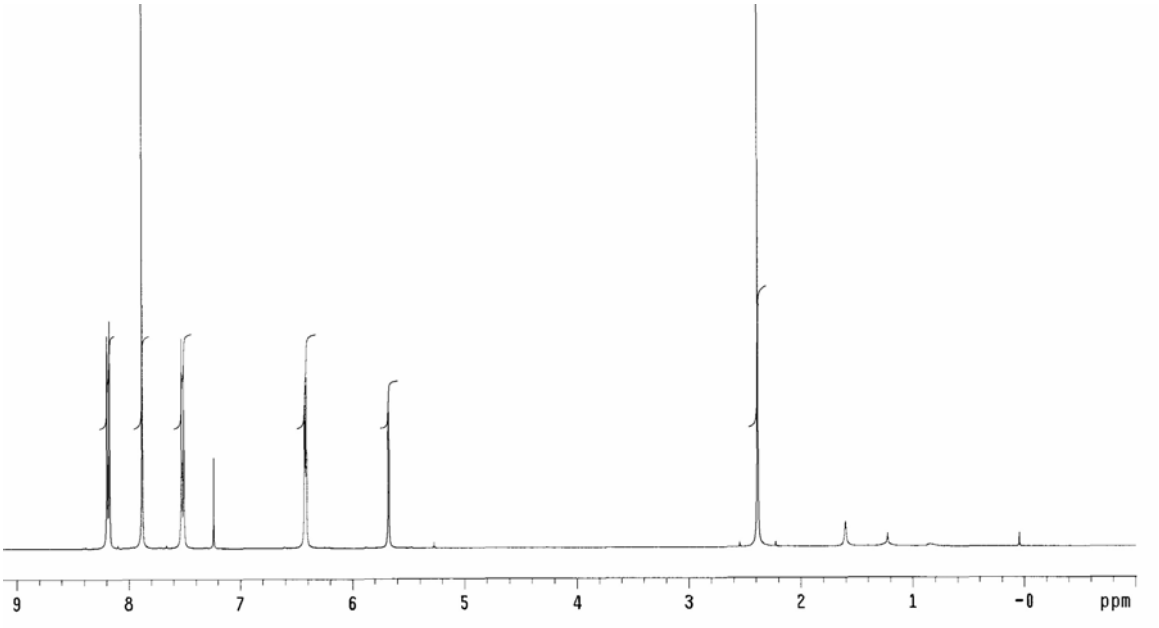
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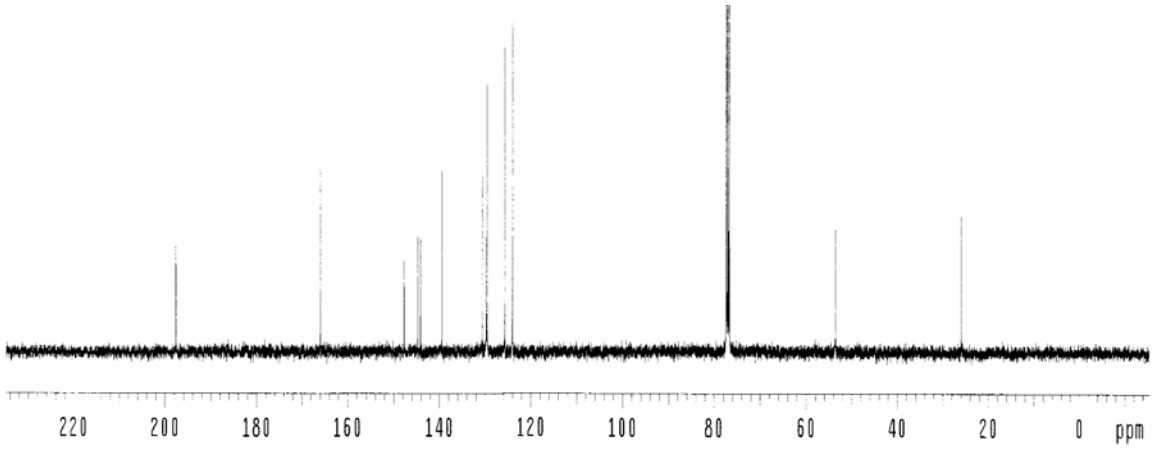
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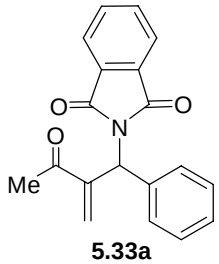

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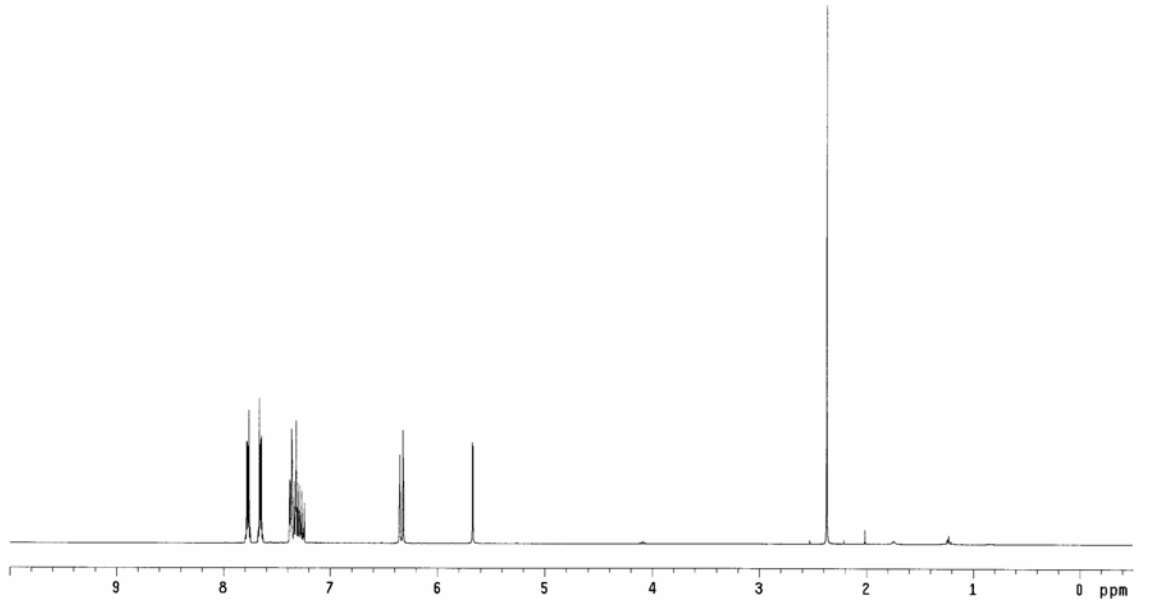

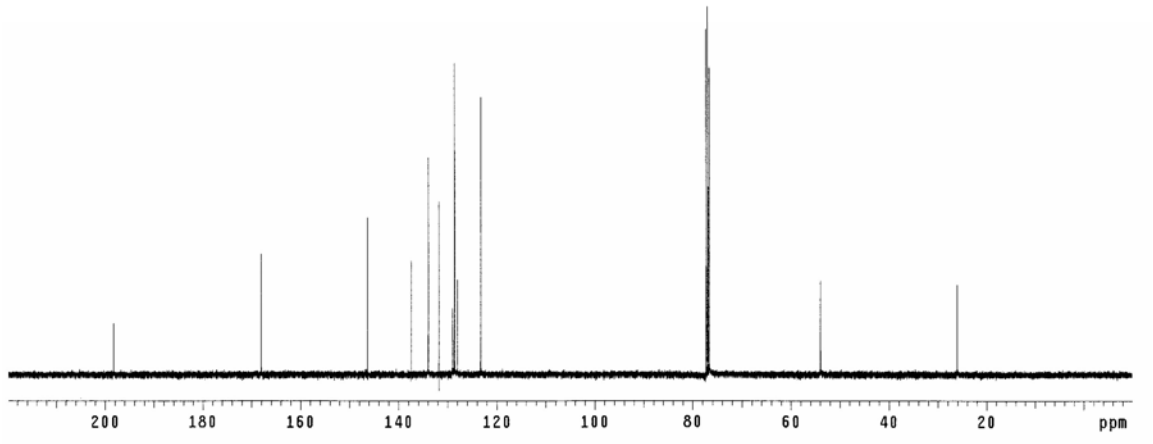

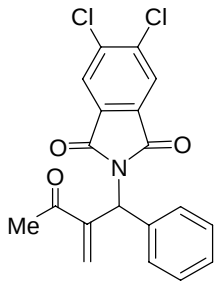
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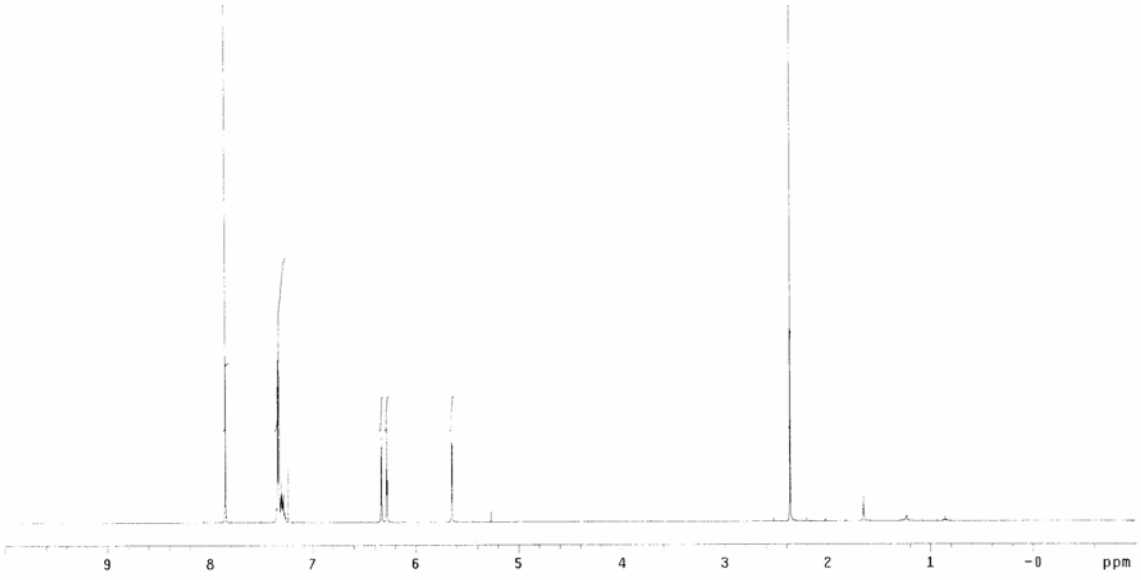
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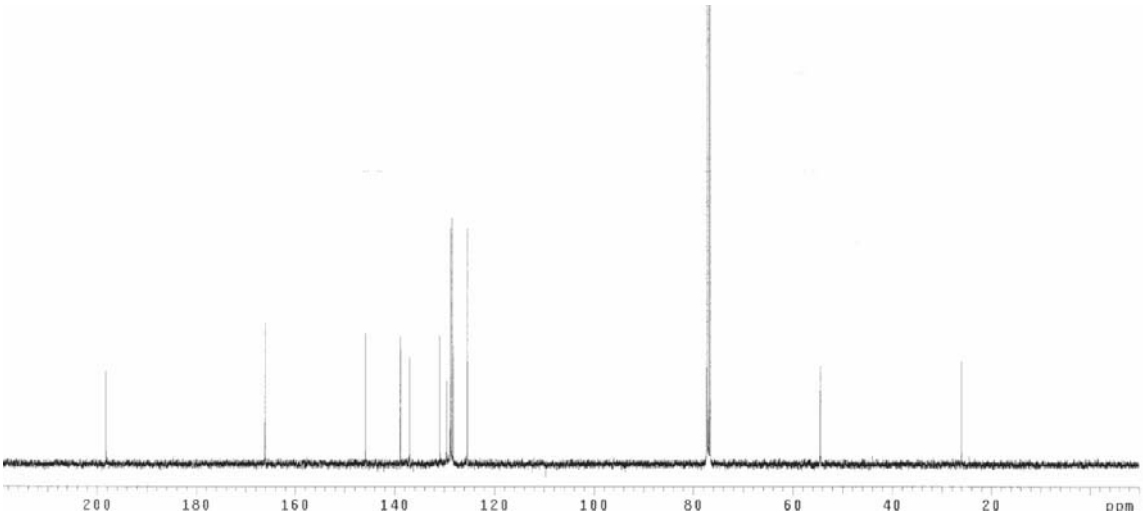
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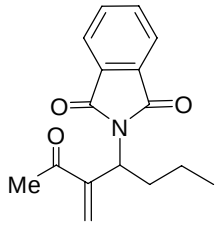

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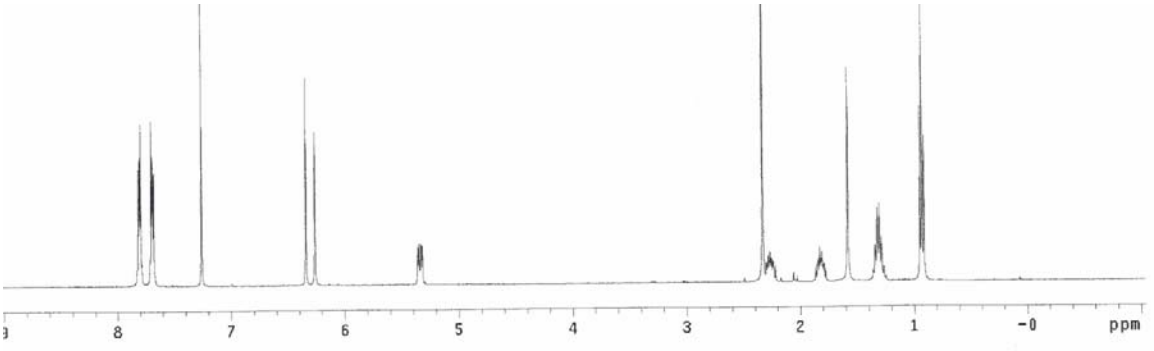

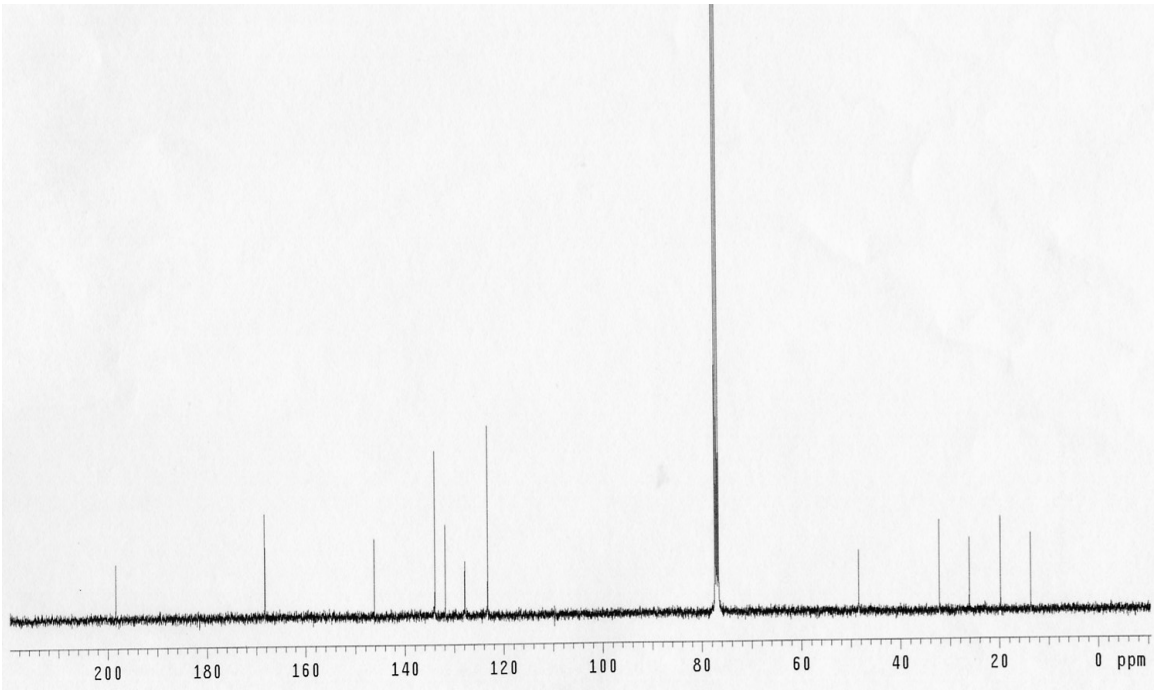

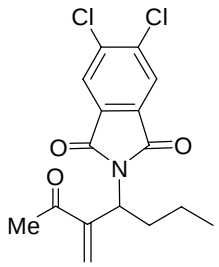
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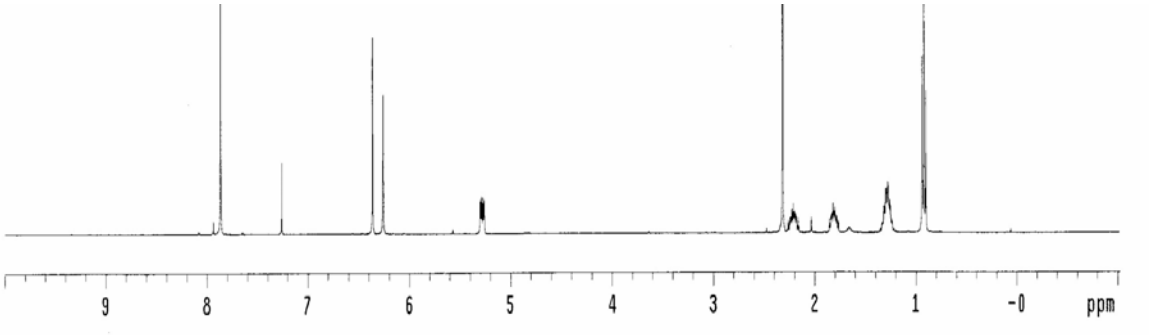
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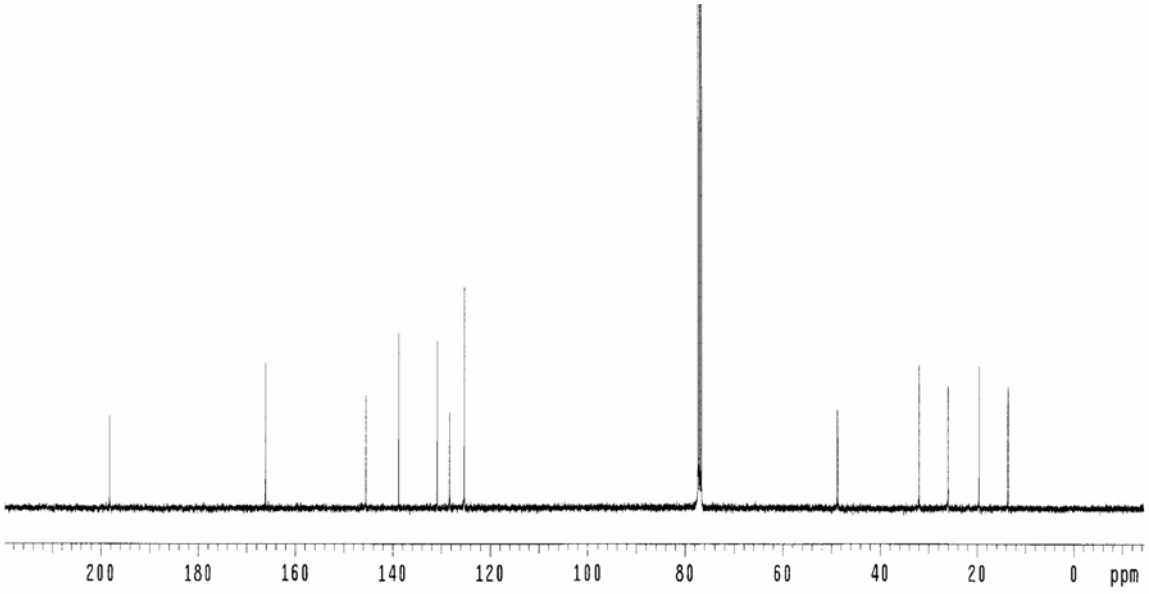
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120
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40
20
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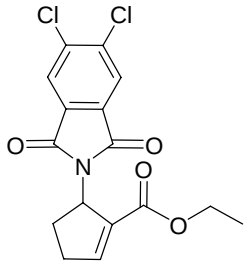

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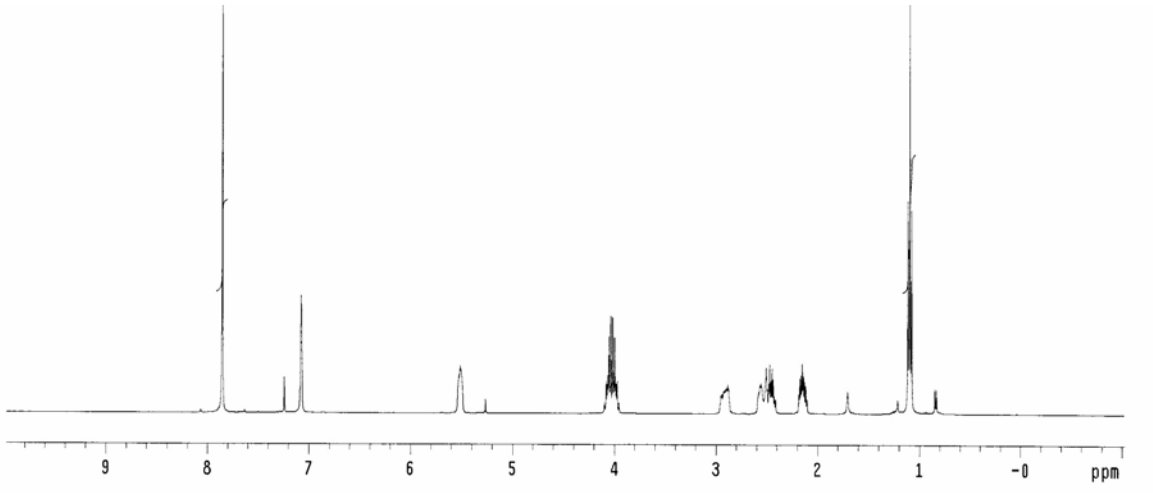

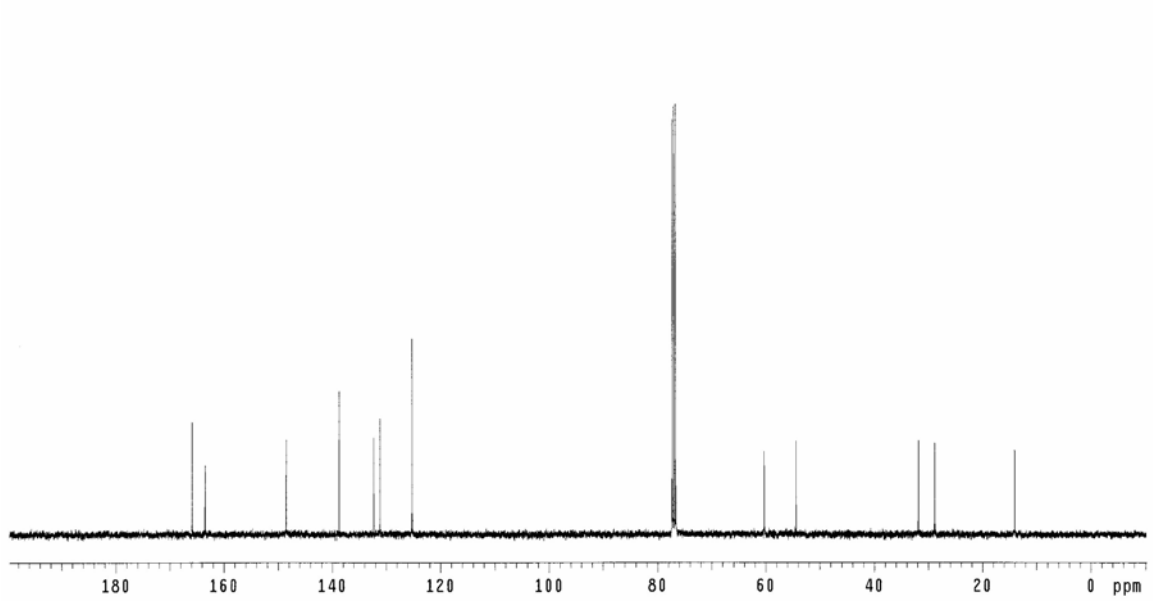

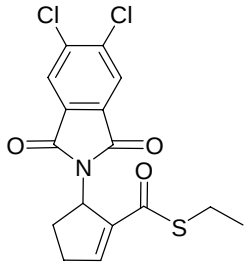

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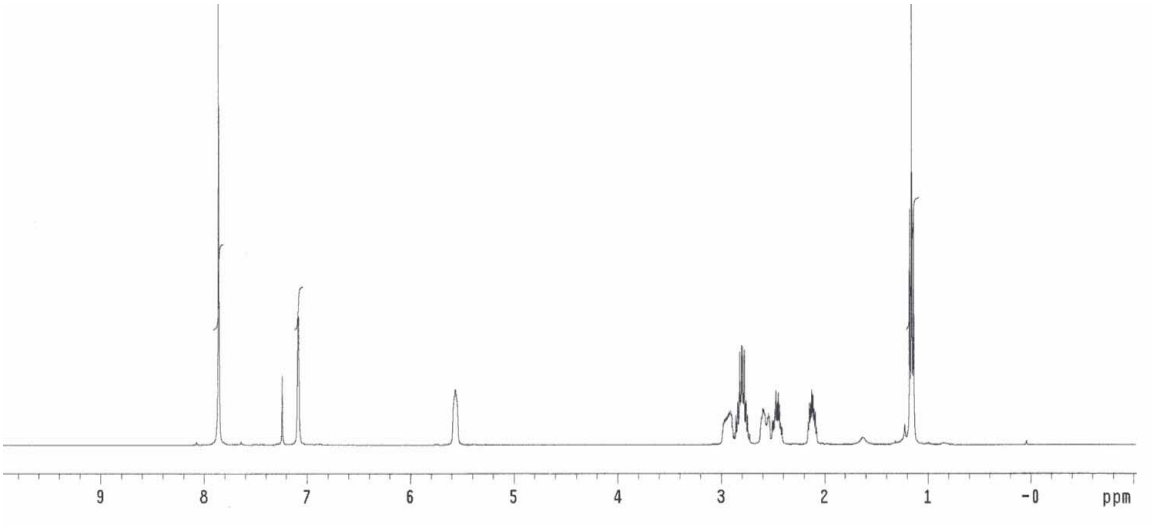

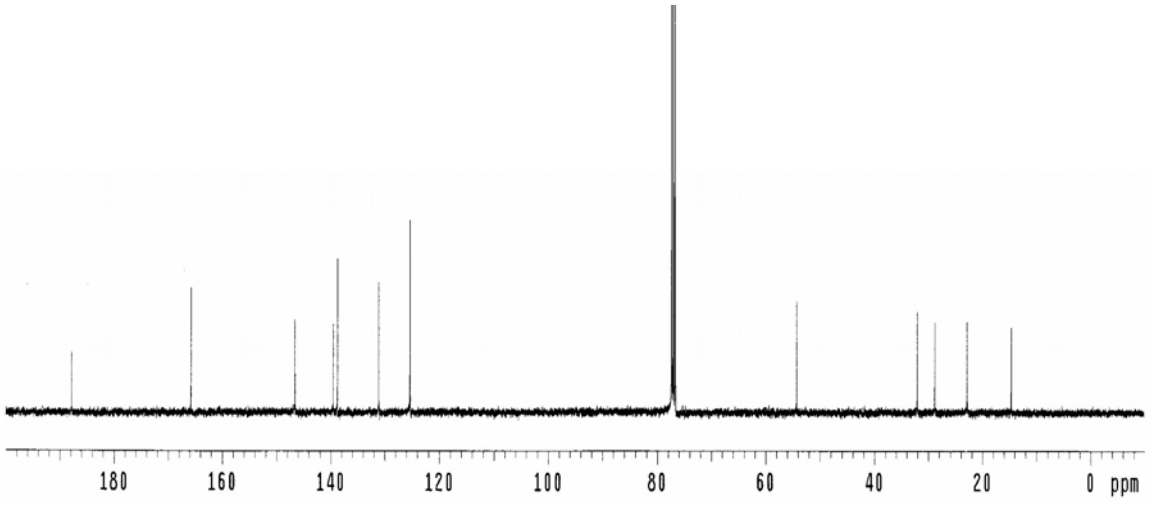

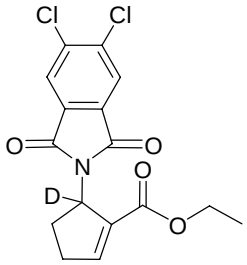

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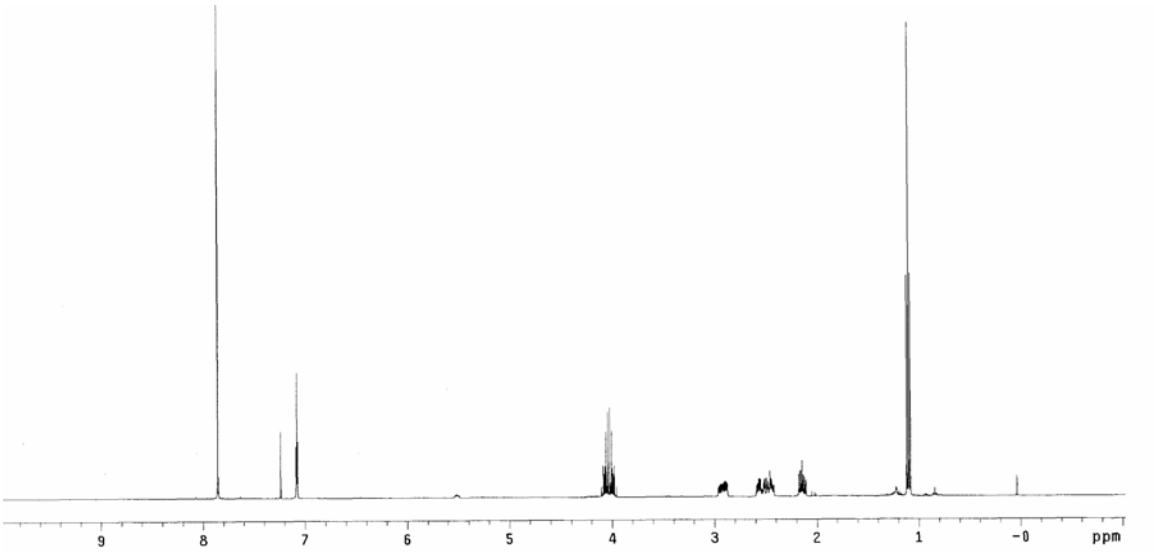

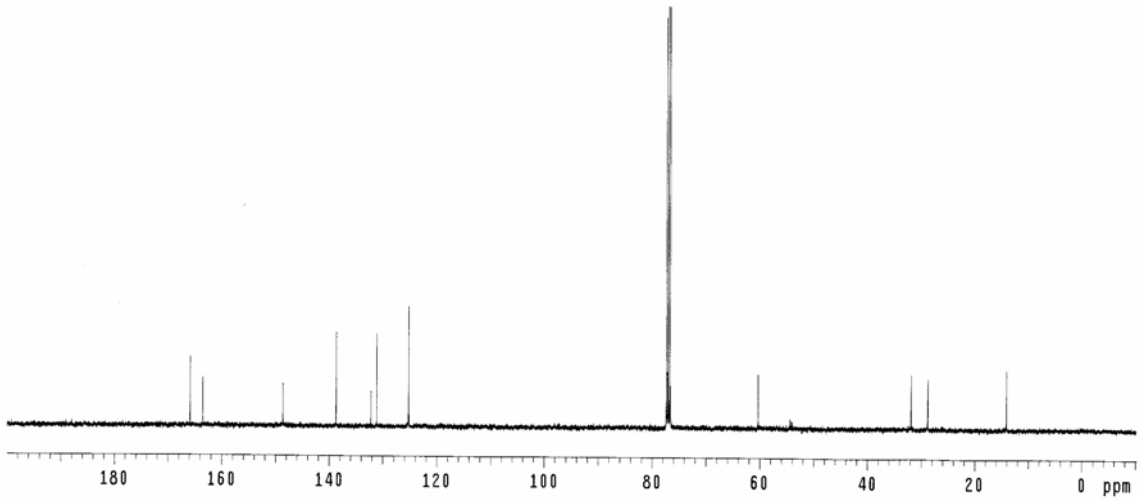

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Vita

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